# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: NDA 19922

## PHARMACOLOGY REVIEW(S)

AUG 8 1996

NDA 19-922

ADDENDUM TO ORIGINAL REVIEW OF NDA 19-922

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

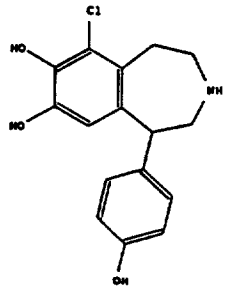
Estela A. González Barry, M.S.
08-30-90, 07-19-96 and 07-26-96

**ORIGINAL SUBMISSION DATES:** 12-12-88 and 06-21-96
**CENTER RECEIPT DATES:** 12-14-88 and 06-25-96
**DIVISION RECEIPT DATES:** 12-09-90 and 06-25-96
**REVIEWER RECEIPT DATES:** 02-08-89 and 06-27-96

**SPONSOR:** Neurex Corporation,
Menlo Park, CA 94025

**DRUG:** Proprietary Name: Corlopam™, injection.
Generic Name: fenoldopam mesylate

Chemical Structure:




Fenoldopam

6-Chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-1H-3-benzazepine-7,8-diol methane sulfonate

MW: 401.87 for the salt.

**PRESENTLY PROPOSED FORMULATION:** Fenoldopam mesylate will be supplied as a solution for intravenous (iv) administration, containing 10 mg/Ml in single-dose vials of 2.5 and 10 ml. Before administration, the formulation must be diluted with 0.9% Sodium Chloride Injection USP or 5% Dextrose Injection USP. Excipients: Sodium Metabisulfite NF; Sodium Citrate, USP; Propylene Glycol, USP; and Water for Injection, USP.

**PHARMACOLOGICAL CLASS:** Vasodilator with postsynaptic dopamine ($DA_1$) receptor agonist activity.

**PROPOSED INDICATION:** For short term treatment of hypertension crisis when oral therapy is not possible.

**RECOMENDED DOSAGE:** The initial dose for fenoldopam is 1.0 mg/hr(≈ 0.24μg/kg/min for a 70 kg patient) administered by continuous i.v. infusion. Increases in the initial infusion rate should not exceed the previously mentioned dose. The maximum recommended dose for fenoldopam is 7.0 mg/h (≈ 1.67 μg/kg/min for a 70 kg patient).

**RELATED INDs:**

**BACKGROUND**: This NDA was originally filed by in 1988. The nonclincial pharmacology and customary toxicology data were reviewed and considered sufficient to support the safety, with several labeling recommendations, of fenoldopam mesylate for human use. However, clinical data were not considered sufficient for approval. And, in 1991 this NDA was withdrawn.

Briefly, in 1993 Nuerex acquired rights to this drug. Neurex is proposing the drug for iv administration for short term treatment in hypertensive crisis. Neurex asserts that the original specifications proposed for fenoldopam mesylate solution for iv infusion ampoule product are "indentical" to those for the vial product originally submitted by with the exception that "the limit for the des-chloro fenoldopam" degradant product has been increased from 0.3% to 0.6% because this is allows for the 0.2-0.3% deschloro fenoldopam formed during the step.

On the proposed label, the maximal prescribed dosage of fenoldopam mesylate in human patients is ≈ 1.67 μg/kg/min for 24 hours. Thus, based on a 0.6% specification for the degradation product the maximal amount that would be administered to a 70 kg patient might be expected to be ≈ 0.01 μg/kg/min.

The firm is relying on the previously submitted/evaluated nonclinical studies with fenoldopam, but has submitted one new iv nonclinical study in rat in wich fenoldopam mesylate containing 2 levels (0.1% and 5%) of the deschloro fenoldopam degradant was given by infusion to rat for 24 hrs. The purpose of this study was to investigate the effects of fenoldopam mesylate with higher levels of the degradant product than those specified for the final drug product.

**NEW NONCLINICAL STUDIES:**

♦ Rat: 24-Hr IV Infusion Study with Fenoldopam Containing Degradant Product Deschloro-fenoldopam (Vol.2)

Testing Facility:

Study Number: TP018VD

GLP Compliance: No statement found.

Animals: Sprague-Dawley (CD-VAF) rats. Both sexes, 10 wks of age. M- 366-427g. F- 219-259g at beginning of study.

Study Design:

Study Design

| Group | Dosage rate (µg/kg/min) | Number of rats |
|---|---|---|
| I | 0 (vehicle; 10% propylene glycol in 0.9% saline) | 6M/6F |
| II | 25 (99.9% + 0.1% | 6M/6F |
| III | 25 (95% + 5% | 6M/6F |

Drug Sponsor's Rationale for Dose Selection

Drug sponsor states that lots of administered in earlier iv toxicology studies contained the degradant product . ' at concentrations ranging from 0.07 to 0.1%.

In the proposed label, the maximal prescribed dosage of fenoldopam mesylate in patients is 1.67 µg/kg/min for 24 hours (≈ 7 mg/hr assuming a 70 kg patient). Specifications for the proposed formulation of fenoldopam are anticipated to include up to 1% of the degradation product Thus, the maximal amount of the degradation product administered to humans would be expected to be ≈ 0.016 µg/kg/min.

Drug sponsor reports that in a previous 24-hour iv infusion studies in rats administered 1 up to 100 µg/kg/min containing 0.1% (or up to 0.01 µg/kg/min) demonstrated medial hemorrhage and necrosis in the arteries of the pancreas, mesentery, stomach, intestine, ovary and kidney; arterial lesions occurred in 50 to 80% of those rats infused with 1, 5, 25, 50 or 100 µg/kg/min for 24 hours. Thus the NOAEL for arterial lesions in rats appears to have been at ≈ 0.1 µg/kg/min. infused for 24 hours. To confirm this observation and as a positive control in this new study, one group of rats received 25 µg/kg/min containing ≈ 0.1% (0.025 µg/kg/min); Group II).

Another group of rats received 25 µg/kg/min containing 5% (or 0.75 µg/kg/min; Group III) to test in the event that concentrations of the degradant is increased to 1%. Thus, rats treated with 25 µg/kg/min fenoldopam containing 5% assessed the effect of a 50-fold increase of (5% vs. 0.1% previously tested).

The 5% concentration of . administered to the rat in conjunction with 25 µg/kg/min fenoldopam equals ≈1.25 µg/kg/min . This dose of is estimated to be ≈ 78 times greater than what would be achieved with infusion of the maximally prescribed dosage of fenoldopam containing 1% of the degradant product (1.25 µg/kg/min vs. 0.016µg/kg/min the maximal amount for a 70 kg patient) in humans.

Mode of Administration of Fenoldopam mesylate/Degradant Product

Fenoldopam mesylate was administered via a tail vein through an indwelling catheter. A constant infusion rate of ≈ 5 µl/min was maintained using an infusion pump. The total volume delivered to each rat in (5 µl/min x 1440 min/24 hrs).

Drug sponsor states that Group I rats (controls) were infused with 10% propylene glycol vehicle prepared by diluting 50% propylene glycol vehicle 1:4 with 0.9% saline.

Daily drug preparation for Group II rats consisted of combining 500 mg fenoldopam (as base), which contained 0.1% with 10 ml of 50% propylene glycol vehicle.

This 50 mg/ml solution was diluted with 1:4 with 0.9% saline in order to prepare a stock solution of fenoldopam which has a concentration of 10 mg/ml in 10% propylene glycol vehicle. To achieve a dosage of 25 µg/kg/min, this stock solution was further diluted with 10% propylene glycol vehicle to obtain the final infusion concentration for each rat based on body weight. (For example, a 0.4 kg rat was infused with a 2 mg/ml solution at a rate of 5 µl/min for 24 hours.)

Group III rats were treated with a solution from Group II to which was added to increase the concentration of the degradant to 5%; this solution was also further diluted to obtain the final infusion concentration based on body weight.

Drug sponsor reported some technical errors were reported with the administration of infusion solutions. However, corrective measures were taken so not to invalidate the study.

Observations and Measurements: These included body weight, physical examination, ophthalmologic examination (once, prior and after cessation of infusion), after cessation of infusion hematology (RBC, WBC, Hgb, HCT, MCV, MCHC and platelets) and clinical chemistry (Na, K, Cl $CO_2$, BUN, Cre, Glu, albumin and several enzymes including AP, AST and ALT (after cessation of infusion). At the end of the study, animals were necropsied and over 40 tissues were collected, over 30 were processed and examined microscopically.

## RESULTS

No rats died. No drug-related clinical signs were reported. No drug-related changes were reported for physical or ophthalmological examinations.

Mean body weights of M and F rats of Groups I, II and III were decreased 10-12% on day 2. Decreases in body weight were attributed to the effects of restraint during infusion, including decreased food and water consumption.

Some hematologic changes were reported; none were significantly different from control values reported. The mean platelet count was decreased 33% below the control mean in Group II rats administered 25 µg/kg/min fenoldopam containing 0.1% This change in was considered by drug sponsor to reflect a difficult venipuncture and/ or responses related to arterial damage induced by the high infusion dosage of fenoldopam.

In some rats in all drug treated groups, mean values for WBC and neutrophil counts were elevated in Group II and Group III (M WBC were decreased), however; these changes were not considered drug related by drug sponsor. Similarly, in mean values of drug treated rats, rats showed decreased lymphocyte counts (20-60%) vs. control values.

Clinical biochemistry changes compared to control were reported in some drug treated rats. These changes included elevated individual mean serum activity in AP, ALT, AST, BUN and carbon dioxide when compared to controls. Drug sponsor stated that these changes had not been reported in previous studies with fenoldopam, and are considered drug-related changes.

Mean serum glucose concentration was decreased 13% and 17% below the control mean in Group II and III male rats, respectively.

Macroscopic observations of irregular, reddened areas along the interlobular artery of the pancreas and branches of the mesenteric artery were interpreted as arterial hemorrhage within the pancreas was observed in 2/6 and 4/6 Group II rats, administered 25 µg/kg/min fenoldopam containing 0.1% This finding was also present in 2/6 and 4/6 Group III rats, administered 25 µg/kg/min fenoldopam containing 5% .

Arterial hemorrhage within the mesentery was present in all rats from Group II and Group III.

A linear, depressed, reddened area in the fundus of the glandular stomach was observed in one M from Group III.

Microscopic Findings: Hemorrhage and medial necrosis of arteries within the pancreas and mesentery, with accompanying periarteritis and perivascular edema, was observed in all drug treated rats (Group II and Group III.) There were no differences between Group II and III rats in the severity of the arterial lesions of the pancreas and mesentery.

Hemorrhage and medial necrosis of arteries within the kidney were observed in 5/6 M and 6/6 F Group II, and 5/6 M and 4/6 F group III. Periarteritis accompanied the renal arterial lesions in 2/6 and 2/6 Group II and III F rats, respectively. The severity of arterial lesions of the kidney was essentially similar between Group II and III rats.

Hemorrhage and medial necrosis of arteries within the serosa of the stomach was present in 5/6 M and 3/6 F rom Group II, and 4/6 M, and 2/6 F from Group III. Periarteritis of the serosa was present in 3/6 M and 5/6 F from Group II, and 3/6 M and 5/6 F from Group III. There were no remarkable differences in the severity of arterial lesions of the stomach.

Hemorrhage and medial necrosis of arteries within the serosa of the colon and/or ileum was observed in 2/6 M and 1/6 F from Group II, and 1/6 Group III M rats. Periarteritis of the colon and/or ileum was observed in 2/6 M and 1/6 F from Group II, and 1/6 Group III M rats. The severity of arterial lesions of the colon and ileum was essentially similar between Group II and III rats.

Periarteritis of the ovary was observed in 1/6 and 2/6 Group II and III F rats, with no difference in the severity of the lesion between the two groups.

Focal erosion and glandular congestion of the fundus of the stomach was observed in one Group III F. This lesion corresponded to the linear, depressed area of the fundus observed macroscopically. A focus of fibrinoid arteritis in the aorta was present in 1 Group III F rat vs. none in controls; this pathologic change was unknown to drug sponsor; it was reported as "not considered" to be drug related.

Hepatic and renal changes were observed in occasional rats from each dosage group. The incidence of the changes did not reflect a treatment-related effect.

Drug sponsor concluded that in the present rat study, the incidence and severity of arterial lesions (hemorrhage and medial necrosis in arteries of pancreas, mesentery, kidney, stomach and intestine accompanied by periarteritis and or/edema) between Group II and Group III rats infused for 24 hrs with fenoldopam mesylated containing either 1% or 5% were comparable indicating that the increased concentration of the _____ did not influence the toxicity profile of drug in rats.

## EVALUATION

Drug sponsor proposes to increase the specifications for the degradation product (descholoro fenoldopam) from 0.3% to 0.6% in the final drug product of fenoldopam mesylate intravenous solution. Drug sponsor asserts that the reason for the proposed increase in the specification is to allow for the 0.2 - 0.3% deschloro fenoldopam formed during the _____ stage.

Drug sponsor reports that lots of fenoldopam mesylate used in earlier nonclinical studies contained deschloro fenoldopam at concentrations ranging from 0.07 up to 0.1%. In support of proposed increased level for the degradant in the final drug product, drug sponsor has conducted one iv study in rat to evaluate the effects of two levels of deschloro fenoldopam in the drug.

Results reported indicate that rats infused intravenously with 25 µg/kg/min fenoldopam mesylate (containing 1 and 5% descholoro fenoldopam) for 24 hrs showed hemorrhage and medial necrosis of the arteries of the pancreas, mesentery, kidney, stomach and intestines accompanied by periarteritis and/or edema; these changes were not seen in the concurrent controls infused with the vehicle. These vascular lesions have been previously reported in rats administered dosages of fenoldopam mesylate ranging from 5 up to 100 µg/kg/min for 24 hrs containing lower levels of deschloro fenoldopam.

The severity of arterial lesions noted were reported as essentially similar between Group II and Group III rats. From the data submitted, it could not be determined at what rat plasma concentrations of drug/degradant product were associated with the reported lesions.

Excipients used in the proposed formulation for fenoldopam mesylate injection have been previously used in approved drugs for iv use. As stated above, the specifications for the drug product include limits for the degradation product expected to occur during the stage. Data submitted on nonclinical study with rats infused with high (5%) levels of degradant were not associated with new or unusual adverse effects not previously seen with fenoldopam mesylate alone.

In the International Conference on Harmonization: Draft Guideline on Impurities in New Drug Products (**54 FR 11268-11272; March 19, 1996**), FDA recommends under "Thresholds for Qualification of Degradation Products in New Drug Products", that for a maximum daily dose of a drug of >100 mg to 2 g, thresholds for qualification of degradation products in new drug products, levels of 0.2% or 2 mg as the total daily intake (TDI); whichever is lower are acceptable. Since the maximum recommended dose for fenoldopam mesylate is 7.0 mg/h [≈ 1.67 µg/kg/min drug might contain up to ≈ 0.10 µg/kg/min of (≈ 0.6%) given to a 70 kg patient], and assuming the drug is infused for 24 hrs, the total amount of fenoldopam mesylate given might be expected to be ≈168 mg containing 1.008 mg of the degradation product*. Thus, the TDI for the degradation product appears to be within the limits recommended in that FEDERAL REGISTER notice.

RECOMMENDATIONS:

1. This NDA is approvable, with some labeling changes, proposed in the previous evaluation of this NDA (see page 53 of Review/Evaluation of Pharmacology and Toxicology Data dated August 1990) and ammended to reflect changes described below.

2. Under "ANIMAL TOXICOLOGY", 2nd paragraph, line 7, delete the term "or cynomolgus monkeys" because data previously reported stated that at least 1 out of 4 cynomolgus monkeys infused fenoldopam 100 µg/kg/min for 24-hr showed intramedial necrosis and/or hemorrhage in arterioles of the gastric submucosa and a branch of the renal artery. Although the intramedial hemorrhage seen in this monkey was qualitatively similar to that reported in rat infused for 24-hr with fenoldopam mesylate, the rat infused with the drug has consistently shown greater organ vessels involvement than the monkey.

3. Under "Carcinogenesis, Mutagenesis and Impairment of Fertility" change the present paragraph to read "The genotoxic potential of fenoldopam was evaluated in the microbial mutagenicity Ames test, point mutation and chromosome aberration assays using Chinese hamster ovary cells, and the micronucleus test in mice. In the *in vitro* chromosomal aberration assay in Chinese hamster ovary cells, the drug was associated with statistically significant and concentration-dependent increase in chromosome aberrations. However, there was no evidence of mutagenic or clastogenic potential with fenoldopam in the other *in vivo* and *in vitro* assays."

* 7 mg/h fenoldopam mesylate X 24-hr infusion= 168 mg TDI. 168 mg X 0.6 degradant= 1.008 mg

4. Under "Pregnancy" delete the term "Teratogenic Effects - Pregnancy..." so that the first words in this paragraph read "Pregnancy category B". After this term, insert the word "Oral" before the sentence "...reproduction studies have been performed.."

Estela A. González Barry, M.S.

cc:
Orig NDA
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HFD-345
HFD-110
HFD-110/RHPM
HFD-110/EBARRY
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NDA # 19-922

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

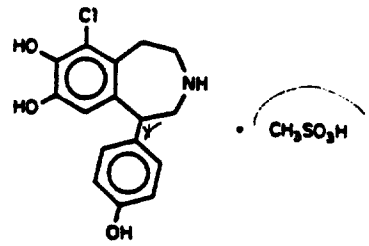
E. Barry, M.S.
08-30-90

ORIGINAL SUBMISSION DATED: 12-12-88
CENTER RECEIPT DATE: 12-14-88
NDA ORIG AMENDMENTS DATED: 12-29-89 and 02-05-90
CENTER RECEIPT DATES: 01-09-90 and 02-09-90
REVIEWER RECEIPT DATES: 02-8-89, 01-09-90 and 02-09-90

SPONSOR:

DRUG:

Proprietary Name: Corlopam™. injection.
Generic Name: fenoldopam mesylate.
Code Name.
Chemical name: 6-chloro-2,3,4,5,-tetrahydro-1-(4-hydroxyphenyl)-1H-3-benzazepine-7,8-diol, methanesulfonate.
Chemical Structure:




MW: 305.76 and 401.87 for the base and salt. respectively.

FORMULATION: Corlopam will be supplied as a solution for intravenous (i.v.) administration, containing 10 mg/mL in single-dose vials of 2.5, 5 and 10 ml. Before administration, the formulation must be diluted with 0.9% Sodium Chloride Injection USP or 5% Dextrose Injection USP.

This formulation contains the following excipients: Sodium Metabisulfite, NF; Citric Acid, USP; Sodium Citrate Dihydrate, USP; Propylene Glycol, USP; Water for Injection, USP and Sterile Nitrogen Gas, NF.

PHARMACOLOGICAL CLASS: Vasodilator with postsynaptic dopamine ($DA_1$) receptor agonist activity.

PROPOSED INDICATION: For the management of hypertension requiring prompt control by i.v. therapy.

PROPOSED DOSAGE: The initial dose is 0.1 mcg/kg/min administered by continuous i.v. infusion. Dosage may be titrated upward as needed by 0.1 mcg increments until an appropriate blood pressure is achieved. Sponsor states that for most patients, titration to a dosage of 0.1 to 0.4 mcg/kg/min produces the target blood pressure.

RELATED INDs:

NONCLINICAL STUDIES:

PHARMACOLOGY

The following are Summary Tables of Pharmacology Studies Provided by Sponsor in this NDA.

Antihypertensive Activity of Fenoldopam

| Preparation Report No.1 | Results | Conclusions |
|---|---|---|
| Intravenous administration in anesthetized spontaneously hypertensive rats; 1.5-15 mcg/kg, [VD 2818] | Decreased blood pressure (12% and 28% at 7.5 and 15 mcg/kg, respectively) with no effect on heart rate | Antihypertensive with no effect on heart rate |
| Oral administration in spontaneously hypertensive rats, 5-25 mg/kg [VD 2811] | Decreased blood pressure 20% with no effect on heart rate | Antihypertensive with no effect on heart rate |
| Oral administration in conscious spontaneously hypertensive rats, 25 mg/kg [VD 2828] | Decreased blood pressure 13% and heart rate 11% | Antihypertensive with little effect on heart rate |
| Intraperitoneal administration in conscious saline-loaded spontaneously hypertensive rats, 50 mg/kg [VD 2832] | Decreased blood pressure 16-24% with variable effects on heart rate (from 17% increase to 13% decrease) | Antihypertensive with little effect on heart rate |

Vasodilating Activity of Fenoldopam

I. Renal Vasodilating Activity

| Experiment Report No.] | Results | Conclusions |
|---|---|---|
| Intravenous administration in anesthetised SHR, 1-15 mcg/kg [VD 2818, VD 2817] | Increases in renal blood flow, decreases in systemic blood pressure | Renal vasodilator which decreases systemic blood pressure |
| Intravenous administration in anesthetised Dahl-SS rats, 10 mcg/kg [VD 2817] | Increases in renal blood flow, small decreases in systemic blood pressure | Renal vasodilator which decreases systemic blood pressure |
| Oral administration in anesthetised SHR, 5-25 mg/kg [VD 2811] | Increases in renal blood flow, decreases in systemic blood pressure | Orally active renal vasodilator which decreases systemic blood pressure |
| Intravenous administration in anesthetised dogs, 3-300 mcg/kg - [VD 2518, VD 2839] | Increases in renal blood flow with only small decreases in systemic blo | Renal vasodilator |
| Intravenous administration in alpha-receptor blocked anesthetised dogs, 0.1-300 mcg/kg [PPS84VD, PPS12VD] | Dose-related increases in renal blood flow and decreases in systemic blood pressure | Renal vasodilator in presence of alpha-receptor blockade |
| Intra-arterial administration in anesthetised dogs, 0.01-3 mcg/kg [VD 2816] | Dose-related increases in renal blood flow and decreases in systemic blood pressure | Renal vasodilator which decreases systemic blood pressure |
| Intraduodenal administration in anesthetised dogs, 1 mg/kg [VD 2839] | Increase in renal blood flow, with small decrease in systemic blood pressure | Renal vasodilator |
| Intravenous administration in conscious dogs, 1-25 mcg/kg [VD 2842, PPS86VD] | Dose-related increases in renal blood flow with variable effect on systemic blood pressure | Renal vasodilator with marginal effect on systemic blood pressure |
| Oral administration in conscious dogs, 0.25-10 mg/kg [VD 2837, PPS83VD] | Dose-related increases in renal blood flow with decreases in systemic blood pressure | Orally active renal vasodilator which decreases systemic blood pressure |

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II. Selectivity for Renal Vasodilating Effect

| Experiment Report No.] | Results | Conclusions |
|---|---|---|
| **Cumulative infusions in anesthetized dogs** | | |
| Fenoldopam, 0.1-810 mcg/kg/min [VD 2525, VD 2539, VD 2515] | Dose-related increases in renal blood flow with only small increases in iliac blood flow | Renal vasodilatory effects tend to occur at lower doses (1-8 mcg/kg) than those required to produce effects on the iliac vasculature (usually > 90 mcg/kg) and systemic blood pressure (usually >270 mcg/kg) |
| Dopamine, 1-40 mcg/kg/min [VD 2525] | Dose-related increases in renal blood flow with little effect on iliac blood flow at low doses but decreases in iliac blood flow at higher doses | Renal vasodilatory effects seen with doses which produce decreases in iliac blood flow |
| **Bolus injections in anesthetized dogs** | | |
| Fenoldopam, 0.1-1.0 mcg/kg [PP0804VD] | Dose-related increases in renal blood flow with tendency toward decreases in iliac blood flow | Renal vasodilatory effects with marginal decreases in iliac blood flow |
| Dopamine, 1.0-8.0 mcg/kg [PP0804VD] | Dose-related increases in renal blood flow and decreases in iliac blood flow | Renal vasodilatory effects at doses which decrease iliac blood flow |
| **Intracoronary injection in anesthetized dogs** | | |
| Fenoldopam, 1 mcg/kg [PP0817VD] | Under conditions of constant coronary perfusion pressure, increase in coronary blood flow | Direct coronary vasodilatory activity |
| Dopamine, 0.01-10 mcg/kg [PP0817VD] | Under conditions of constant coronary blood flow, dose-dependent increase in perfusion pressure; under conditions of constant coronary perfusion pressure, dose-dependent increase in coronary blood flow. | Direct coronary vasodilatory activity |

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Summary of Renal Function Studies in Conscious Dogs

| Experiment | Report No.] | Results | Conclusions |
|---|---|---|---|
| Intravenous infusion in phosphate-mannitol infused dogs, 0.05-20 mcg/kg/min [VD 2526, VD 2516] | | Dose-related increases in ERPF; tendency toward decreased GFR; no effect on electrolyte excretion | Increase in ERPF with little effect on renal function |
| Oral administration in phosphate-mannitol infused dogs, 1-20 mg/kg [VD 2516, VD 2522, VD 2546, VD 2883, VD 2887, VD 2845, VD 2528] | | Dose-related increases in ERPF; small, variable effects on GFR; variable effects on electrolyte excretion but tendency toward increase | Increase in ERPF with little effect on renal function |
| Intravenous infusion in sodium chloride infused dogs, 0.05 mcg/kg/min [VD 2543] | | Increase in ERPF with no effect on GFR or electrolyte excretion | Increase in ERPF with no effect on renal function |
| Oral administration in dextrose infused dogs, 2.5-10 mg/kg [VD 2524, VD 2886, PP881VD, PP882VD] | | Dose-related increases in ERPF; small, variable increases in GFR; increase in $Na^+$ and $K^+$ excretion | Increase in ERPF with little effect on renal function |

Comments:

Fenoldopam is a racemic mixture of two R- and S-optical enantiomers. The R-enantiomer is reported to be more potent than the racemate. [The renal and systemic vasodilator activities are properties of the R-enantiomer;] these activities are antagonized the DA-1 antagonist SK&F R-83566 but not the DA-2 antagonist domperidone. The S-enantiomer is essentially inactive.

Although some of the preclinical pharmacology studies were conducted with the hydrobromide salt of fenoldopam ( , the more soluble mesylate salt was used for most of the preclinical and the clinical studies.

In rat (SHR or Dahl-SS) and dog, fenoldopam administered by oral and i.v. routes decreases blood pressure due to its renal vasodilatory action. In dog, the drug shows a direct coronary vasodilatory activity. [The mechanism of vasodilation appears to be predominantly stimulation of $DA_1$ receptors. Although in dog fenoldopam produces renal vasodilation and an increase in renal plasma flow (RPF), there is variable increase in glomerular filtration rate and urine volume and there is no remarkable effect on electrolyte excretion. Thus, in dog, fenoldopam appears to have little effect on kidney function.]

Oral administration of fenoldopam increased plasma renin activity in conscious male beagle dogs. Published literature provided by the sponsor reports that in dog, administration of fenoldopam is also associated with elevation of aldosterone activity. In anesthetized vagotomized rat, i.v. administration of the angiotensin converting enzyme inhibitor captopril antagonized the pressor activity of angiotensin I in a dose-related manner. This antagonism was selective in that comparable pressor activity produced by angiotensin II was not similarly antagonized by captopril. In these rats, i.v. administration of fenoldopam did not inhibit pressor responses to angiotensin (I or II) suggesting that the drug causes no inhibition of angiotensin converting enzyme.

Summary of Effects of Fenoldopam on Adrenergic Neuroeffector Systems.

Fig. A is a representation of an arterial neuroeffector junction displaying the location of adrenergic receptor subtypes.

| Preparation | Report No.] | Results | Conclusions |
|---|---|---|---|
| **Postjunctional Alpha and Beta Adrenergic Receptors** | | | |
| Pithed rat | [VD 2824, VD 2838] | No effect on MAP or HR (1-288 mcg/kg i.v.) | Not alpha agonist |
| Isolated perfused rabbit ear artery | [VD 2838] | No constrictor activity (up to 38 uM); weak inhibition of NE above 18 uM | Not alpha$_1$ agonist; weak alpha$_1$ antagonist |
| Rabbit aortic rings | [PPS11VD] | Antagonism of NE, $pK_B$ = 5.41 | Weak alpha$_1$ antagonist |
| Dog saphenous vein | [PPS11VD] | Non-competitive antagonist of alpha$_1$ agonist methoxamine (apparent $pK_B$ = 5.8) | Weak alpha$_1$ antagonist |
| Radioligand receptor binding with rat cortex | [77P] | Displaced $^3$H-WB4101 ($K_{bind}$ = 0.942 nM) | Weak alpha$_1$ antagonist |
| Guinea-pig right atrium | [VD 2827, VD 2514] | Small increases in rate which were abolished by reserpine pretreatment (0-38 uM) | Not beta agonist |
| Guinea-pig papillary muscle | [VD 2513] | No inotropic or arrhythmogenic activity (0.3-758 uM) | Not beta agonist |
| Guinea-pig tracheal chain | [VD 2828] | No relaxation of spontaneous tone (0.84-298 uM) | Not beta agonist |
| Radioligand receptor binding | [77P] | Displaced $^3$H-clonidine (rat cortex; $K_{bind}$ = 0.838 uM) Displaced $^3$H-yohimbine (human platelet; $K_{bind}$ = 0.839 uM) | Interacts with alpha$_2$ receptors |
| Isolated field stimulated guinea-pig ileum | [PPS11VD] | Competitive antagonist of alpha$_2$ agonist B-HT 920 ($pK_B$ ≥ 7.68) | Alpha$_2$ antagonist |
| Isolated dog saphenous vein in vitro | [PPS11VD] | Competitive antagonist of alpha$_2$ agonist B-HT 920 ($pK_B$ ≥ 7.78) | Alpha$_2$ antagonist |
| Dog pulmonary vascular tone | [PPS89VD] | Antagonised effects of alpha$_2$ agonist B-HT 933 (38-388 mcg/kg/min) | Alpha$_2$ antagonist |
| Electrical stimulation of renal nerve plexus in anesthetised dogs | [VD 2857] | Electrically-stimulated vasoconstriction not inhibited (1 mcg/kg/min) | Not DA$_2$ agonist |
| Isolated perfused rabbit ear artery | [VD 2838] | Inhibition of constriction elicited by periarterial nerve stimulation ($EC_{88}$ = 1.2 uM); not blocked by haloperidol or metoclopramide | Not DA$_2$ agonist |
| Radioligand receptor binding | [77P] | Displaced $^3$H-spiroperidol (rat striatum; $K_{bind}$ = 0.595 nM) | Weak interaction with DA$_2$ receptors |
| Isolated superfused guinea pig atria | [VD 2838] | Little effect on inotropic responses to electrical stimulation (0.3-38 uM) | Not prejunctional alpha agonist |

Summary of Effects of Fenoldopam on Adrenergic Neuroeffector Systems(Cont'd).

| Preparation | Report No.] | Results | Conclusions |
|---|---|---|---|
| **Dopamine and Alpha$_2$-Adrenergic Receptors** | | | |
| Rabbit splenic artery | [PPS11VD, VD 2868] | Relaxation of NE-induced contractions ($EC_{50}$ = 1-8 uM); antagonized by $DA_1$ antagonists | $DA_1$ agonist |
| Rabbit isolated perfused mesenteric-ileal vascular bed | [184P] | Relaxed $K^+$-constricted vessels ($EC_{50}$ = 8 uM); antagonized by SKF R-83566 | $DA_1$ agonist |
| Rabbit kidney arterioles | [84P] | Relaxed NE-contracted afferent and efferent arterioles ($EC_{50}$ = 8.14and 8.15 uM, respectively); antagonized by SKF R-83566 | $DA_1$ agonist |
| Preganglionic electrical stimulation of cardiac sympathetic nerves in dogs | [VD 2868, PPS18VD] | Inhibited tachycardia induced by by preganglionic stimulation (18, 38, 188 mcg/kg/min); effect blocked by $DA_1$ antagonist | $DA_1$ agonist |
| Opossum lower esophageal sphincter muscle | [VD 2869] | Produced marginal relaxation ($EC_{50}$ = 188 uM) | DA agonist; receptor subtype not clear |
| Radioligand receptor binding with rat striatum | [75P] | $^3$H-fenoldopam binds specifically and saturably ($K_D$ = 8.8823 uM, $B_{max}$ = 595 fmol/mg protein) | Interacts with $DA_1$ receptors |
| Preganglionic stimulation in dog autoperfused hindlimb | [VD 2868, PPS18VD] | Inhibited vasoconstriction induced by stimulation of preganglionic sympathetic fibers and alpha$_2$ agonist B-HT 928 (3 mcg/kg/min); effect antagonized by $DA_1$ antagonist | $DA_1$ agonist Alpha$_2$ antagonist ✓ |

Summary of Receptor Binding Data

| Receptor Type | Preparation [Reference] | Receptor Binding Constant (nM) |
|---|---|---|
| $DA_1$ | Rat striatum, $^3$H-fenoldopam binding [75P] | 2.3 |
| $DA_2$ | Rat striatum, displacement of $^3$H-spiroperidol binding [77P] | 595. |
| Alpha$_1$ | Rabbit aortic rings [PPS11VD] | 3988. |
| | Dog saphenous vein [PPS11VD] | 148. |
| | Rat cortex, displacement of $^3$H-WB4101 binding [77P] | 942. |
| Alpha$_2$ | Isolated field stimulated guinea-pig ileum [PPS11VD] | 25. |
| | Dog saphenous vein [PPS11VD] | 17. |
| | Human platelet, displacement of $^3$H-yohimbine binding [77P] | 39. |
| | Rat cortex, displacement of $^3$H-clonidine binding [77P] | 38. |

Results of the above studies indicate that fenoldopam has a greater affinity for $DA_1$ receptors than for $DA_2$ or alpha-adrenergic receptors. The drug demonstrated alpha-2-adrenergic receptor antagonist activity, very weak alpha-1-adrenergic receptor antagonism and no beta-adrenergic agonist activity.

## Summary of General Pharmacodynamic Studies.

| Test | Species | Dose Range and Route | Principal Findings | Report |
|---|---|---|---|---|
| **Central Nervous System** | | | | |
| Anticonvulsant activity: Minimal electroshock | mouse | 25, 100 mg/kg po | Inactive | VD 2510 |
| Maximal electroshock | mouse | 25, 100 mg/kg po | Inactive | VD 2502 |
| Confined motor activity | rat | 200 mg/kg po | 45% reduction at 120 min post dose | VD 2505 |
| Tryptamine-induced convulsions | rat | 200 mg/kg po | No potentiation | VD 2504 |
| Reserpine-induced ptosis | rat | 50 mg/kg po | Not prevented | VD 2503 |
| | | 10 mg/kg ip | Not prevented | VD 2503 |
| MAO activity | rat | 0.1-100 uM | No inhibition of brain or liver MAO | VD 2042 |
| Rotation in rats with unilateral lesions of the the substantia nigra | rat | 2-10 mg/kg ip | No significant contra-lateral rotation | VD 2509 VD 2529 |
| | | 0.1-3.8 mcg/rat into caudate | Dose-related rotation | |
| Adenylate cyclase activity | rat | 0.001-100 uM | Concentration-related stimulation, $EC_{50}$ = 0.039 uM; maximal effect 65-80% of that seen with dopamine ($EC_{50}$ = 4 uM); marginal (16-28%) inhibition of stimulation of dopamine-stimulated adenylate cyclase at 1-100 uM | VD 2023 VD 2537 VD 2548 VD 2519 |
| Polyestradiol-stimulated prolactin release | rat | 2, 10 mg/kg ip | No effect on increase in serum prolactin levels | VD 2041 |
| Discriminative stimulus | rat | 0.125-1.0 mg/kg ip | Not effective as discriminative stimulus | 110P 16P |
| Stereotypy | rat | >15 mg/kg sc | Did not influence stereotypies induced by $DA_2$ agonist quinpirole | 17P |
| **Autonomic Nervous System** | | | | |
| Effect on blood pressure responses to autonomic stimuli | dog | 4.2-538.5 mcg/kg iv | No effect on pressor responses to NE, tyramine, or DMPP; depressor responses to furfuryl trimethylammonium, histamine, isoproterenol, peripheral vagal stimulation; the tachycardic response to isoprenaline; recovery from head-up tilt hypotension | VD 2033 |

## General Pharmacodynamic Studies (Cont'd).

| Test | Species | Dose Range and Route | Principal Findings | Report |
|---|---|---|---|---|
| **Cardiovascular System** | | | | |
| Infusions in rats | rat | 100 mcg/kg/min | 3 hr infusion: no effect on MAP or HR<br>6 or 24 hr infusions: decrease in MAP (15-20%); no evidence for tolerance to hypotensive effect | VD 2063<br>VD 2046 |
| | | 2.5-160 mcg/kg/min | 15 min infusions at each rate: fall in MAP, increase in HR; MAP response waned by >60% by end of infusion | 121P |
| General hemodynamics in anesthetized dogs | dog | 25, 50 mcg/kg iv | Modest (10-30%), non-dose-related decreases in MAP, HR, TPR, coronary flow, coronary vascular resistance, and dP/dt; slight increase in left ventricular end-diastolic pressure at 25 mcg/kg; no change in aortic flow | VD 2025 |
| Effect on electrocardiogram | dog | 75 mcg/kg/min | 6 hr infusion: no changes in ECG other than moderate tachycardia | VD 2501 |
| | | | Daily, 5 days: no effect on ECG or HR at 5 mg/kg, moderate tachycardia but no other change in ECG at 25 mg/kg | VD 2501 |
| Effect on blood pressure and heart rate in conscious | dog | 25 mg/kg po | Daily, 3 days: decreased BP (20-30%) and increased HR (30-130%) for 90-120 min after each dose; emesis in 3 dogs after most but not all doses, usually within first hr post dose | VD 2029 |
| Congestive heart failure | rabbit | 10 mcg/kg/min | CHF induced with adriamycin; decrease in MAP and TPR, increase in CO and blood flow to kidneys, small intestine, and brain | 106P |
| Effect on platelet function in platelet-rich plasma | human | 0.3-60 uM | 60 uM: did not induce platelet aggregation; 30 uM: did not inhibit platelet aggregation induced by arachidonic acid or, in most exps., by ADP, collagen, or thrombin; competitively inhibited epinephrine-induced platelet aggregation | VD 206 |
| **Respiratory system** | | | | |
| Pulmonary resistance and dynamic lung compliance | dog | 50 mcg/kg iv | No effect on pulmonary resistance or dynamic lung compliance | VD 2040 |
| Pulmonary hemodynamics in auto-perfused lung preparation | dog | 1-100 ug | Injected into perfused pulmonary circulation: little or no effect on perfusion pressure, but dose-dependent fall in MAP and increase in RBF | 183P<br>190P |
| Pulmonary hemodynamics | newborn lamb | 1.4-337 mcg/kg iv | Increase in pulmonary pressure at 337 mcg/kg; potentiation of vasoconstriction induced by hypoxia | 58P<br>59P<br>62P |

## General Pharmacodynamic Studies (Cont'd).

| Test | Species | Dose Range and Route | Principal Findings | Report |
|---|---|---|---|---|
| Gastrointestinal system<br>Intestinal motility | mouse | 100 mg/kg po | Reduced fecal pellet count by 2.2% | VD 2500 |
| Pylorus-ligated rat | rat | 50 mg/kg po | No effect on pH or volume of gastric secretion | VD 2508 |
| Anesthetized lumen-perfused rat | rat | 10 mcg/kg/min | No effect on pentagastrin-induced acid output | 158P |
| Gastric irritation | rat | 200 mg/kg po | Microscopic signs of gastric irritation in only 1 of 8 rats | VD 2511 |
| Mucosal damage in ex-vivo gastric chamber | rat | in vitro | Did not reduce mucosal blood, fluid, or albumin loss after gastric ischemia or topical aspirin (20 mM + 100 mM HCl) | 158P |
| Gastric and duodenal blood flow | rat | 10 mcg/kg/min | No effect on gastric blood flow but duodenal blood flow increased | 158P |

Comments:

When administered p.o. or i.p., fenoldopam exhibited no remarkable effects on CNS or gastrointestinal system of mouse or rat. In in vitro preparations, fenoldopam was a stimulant of cAMP production in rat caudate homogenate and showed no MAO inhibition in rat brain or liver. In anesthetized mongrel dog, fenoldopam over a dose range of about 21-530 mcg/kg i.v. did not produce significant alteration of MABP responses to standard agonists and test procedures, or isoproterenol-induced tachycardia demonstrating no effect on the autonomic nervous system. Fenoldopam exhibited no remarkable effects on the respiratory system of the dog. In anesthetized dog, a dose of 50 mcg/kg i.v (infused over 10 min) had no effect on pulmonary resistance or dynamic lung compliance. Published literature provided by the sponsor reports that intraarterial administration of fenoldopam directly into the pulmonary circulation of dog resulted in reduction in renal vascular resistance at doses that had no remarkable effects on pulmonary vascular resistance.

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Summary of Drug Interaction Studies

| Combination Drug | Species | Results | Report |
|---|---|---|---|
| Hydralazine | Rat | Hypotension no greater with combination than with hydralazine alone; no overt deleterious effects | VD 2063 |
| Sodium nitroprusside | Rat | Hypotension no greater with combination than with sodium nitroprusside alone; no overt deleterious effects | VD 2063 |
| Phenoxybenzamine | Rat | 15-20% decrease in blood pressure; combination well tolerated; no overt deleterious effects | VD 2063 |
| Hydrochlorothiazide | Rat | Combination usually produced greater increases in urine output than hydrochlorothiazide alone | VD 2015 |
| Hydrochlorothiazide | Dog | Greater increases in ERPF, GFR, and urinary $Na^+$ excretion with combination than with HCT alone | VD 2001<br>VD 2002 |
| Triamterene | Dog | Increase in ERPF not different from that with fenoldopam alone but greater than with triamterene alone; increase in urinary $Na^+$ excretion not different from triamterene alone; effect of triamterene on urinary $K^+$ excretion reduced by the combination | VD 2004<br>VD 2005<br>VD 2007<br>VD 2008<br>VD 2009 |
| Propranolol | Dog | Propranolol had no effect on ERPF or GFR; urinary $Na^+$ increased; increase in plasma renin activity less than with fenoldopam alone | VD 2054<br>VD 2530 |
| Dobutamine | Dog | Greater increase in renal blood flow with fenoldopam than with dobutamine alone without significant effects on increases in contractile force produced by dobutamine | 119P |
| Captopril | Dog | Combination produced no synergistic effect on blood pressure or heart rate | PP014VD |
| Captopril | Dog | Fenoldopam had no effect on responses to captopril; increase in RBF greater with combination than with fenoldopam alone at 0.1 mcg/kg/min but not at 3 mcg/kg/min | VD 2019 |
| Captopril | Dog | Combination produced greater increase in ERPF than fenoldopam alone | VD 2045 |
| RS-10085 | Dog | Combination resulted in 2-fold potentiation of the natriuretic and kaliuretic effects of either agent alone | 166P |
| Cephalothin | Dog | Fenoldopam had no effect on serum half-life of cephalothin | VD 2052 |
| Halothane | Rat | No significant interactive effects on cardiovascular function | 67P |
| Halothane | Dog | Fenoldopam shown to produce increase in renal blood flow in the presence of hypotension induced by sodium nitroprusside while under halothane anesthesia | 18P<br>19P |
| Isoflurane | Rat | No significant interactive effects on cardiovascular function | 67P |

Comments:

In rats and dog, fenoldopam in combination with drugs likely to be used in clinical situations (e.g. hydrochlorothiazide, hydralazine, sodium nitroprusside, phentolamine, captopril or propranolol) produced additive effects or effects similar to those expected for either drug alone; there were no adverse drug interactions.

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TOXICOLOGY

Summary/evaluations of toxicology studies previously submitted were performed by previous pharmacologists.

The following are Summary Tables of Toxicology Studies Provided by Sponsor in this NDA. (Studies were conducted in Sponsor's Laboratories).

1. Tabulation of Single Dose Toxicity Studies.

| Species | Strain | No./Group | Mode of Administration | Doses | Study Duration |
|---|---|---|---|---|---|
| Mouse | CF1 | 10M | I.V. Bolus | 15.0, 20.5, 27.4, 37.4, 49.8 mg/kg | 10 days |
| Mouse | CF1 | 10F | I.V. Bolus | 15.0, 20.5, 27.4, 37.3, 49.8 mg/kg | 10 days |
| Mouse | CF1 | 10M | Oral Gavage | 400, 600, 900, 1350, 2000 mg/kg | |
| Mouse | CF1 | 10F | Oral Gavage | 400, 600, 900, 1350, 1999.9, 3000 mg/kg | 10 days |
| Rat | CR CD* | 10M | I.V. Bolus | 25, 31, 39, 50 mg/kg | 10 days |
| Rat | CR CD | 10 or 20F | I.V. Bolus | 20.0, 26.2, 34.5, 45.5, 60.0 mg/kg | 10 days |
| Rat | CR CD | 10M | Oral Gavage | 498.5, 658.8, 867.3, 1156.4, 1495.4 mg/kg | 10 days |
| Rat | CR CD | 10F | Oral Gavage | 400, 540, 715, 990, 1300, 1730 mg/kg | 10 days |

* CR CD = Charles River caesarean derived rats

- Results:

| Route | Species | | $LD_{50}$ mg/kg (95% confidence limits) | Salt Equivalent mg/kg |
|---|---|---|---|---|
| I.V. | Mouse | M | 28.9 (24.3-34.4) | 38.0 |
| | | F | 37.0 (30.1-45.5) | 48.6 |
| I.V. | Rat | M | 38.0 (31.9-45.2) | 49.9 |
| | | F | 50.3 (41.9-60.4) | 66.1 |
| P.O. | Mouse | M | 1261. (876-1816) | 1657. |
| | | F | 1400. (1120-1750.1) | 1839.7 |
| P.O. | Rat | M | 797.5 (681.7-993.1) | 1048. |
| | | F | 970.0 (763.8-1231.9) | 1274.6 |

After i.v. administration of fenoldopam, a remarkable acute toxic effect seen in both rat and mouse was respiratory distress. At doses above 1000 mg/kg p.o. tremors and convulsions were reported.

2. Tabulation of Repeated Dose Subacute and Chronic Toxicity Studies.

| Species | Strain | No./Group | Mode of Administration | Doses* | Study Duration |
|---|---|---|---|---|---|
| SUBACUTE: | | | | | |
| Mouse | CD1 | 10M, 10F | Oral Gavage | 6.25, 12.5, 25, 50,75,100,150,200 mg/kg/day | 3 months |
| Rat** | CR CD | 12M, 12F | I.V. Bolus | 2, 8, 16-20 mg/kg/day | 2 weeks |
| Rat | CR CD | 8M, 8F | I.V. Infusion | 5, 25, 50/100 mcg/kg/min | 24 hours |
| Rat | CR CD | 8M, 8F | I.V. Infusion | 0.1, 1.0 mcg/kg/min | 24 hours |
| Rat | CR CD | 10M | Oral Gavage | 38.1, 76.1, 152.2, 304.4 mg/kg/day | 11 days |
| Rat | CR CD | 10F | Oral Gavage | 38.1, 76.1, 152.2, 304.4 mg/kg/day | 10 days |
| Rat | CR CD | 15M, 15F | Oral Gavage | 25-15-25, 50-30-50, 100-130-0-75-0-60-75-100-115 mg/kg/day | 3 months |
| Dog | Beagle | 2M, 2F | I.V. Bolus | 0.5, 1.0, 2-4-8 mg/kg/day | 6 days |
| Dog | Beagle | 1M, 1F | I.V. Infusion | 1, 5, 25, 75, 150 mcg/kg/min | 6 hours |
| Dog | Beagle | 2M, 2F | I.V. Infusion | 5, 50, 100 mcg/kg/min | 24 hours |
| Dog | Beagle | 3M, 3F | I.V. Infusion | 5, 50, 100 mcg/kg/min daily for 6 hours | 14 days |
| Dog | Beagle | 1M, 1F | I.V. Infusion | 2.5-10-20-50-70-100 mcg/kg/min of dopamine | 5.5 hours |
| Dog | Beagle | 3M | I.V. Infusion | 2.5, 20, 50 mcg/kg/min of dopamine | 12 hours |
| Dog | Beagle | 3M, 3F | Oral Capsule | 6.25, 12.5-15-18, 25-30-36-42-48 mg/kg/day*** | 3 months |
| Monkey | Cynomolgus | 1-2M | I.V. Infusion | 5, 100 mcg/kg/min | 24 hours |
| Monkey | Cynomolgus | 4M | I.V. Infusion | 5, 50, 100 mcg/kg/min | 24 hours |
| CHRONIC: | | | | | |
| Rat | CR CD | 20M, 20F | Oral Gavage | 15, 25, 40 mg/kg/day | 12 months |
| Dog | Beagle | 4M, 4F | Oral Capsule | 10, 20-25, 40-50-65-75-85-100-120 mg/kg/day**** | 1 year |

* Doses administered in chronologic order to a single group during the course of the study are indicated as xx-xx-xx.
** CR CD = Charles River caesarean derived rats; CR NZW = Charles River New Zealand White rabbits

*** The mid-dose was increased on days 15 and 36 and the high-dose was increased on days 15, 36, 64 and 78 of study.
**** The mid-dose was increased on day 36 and the high-dose was increased on days 36, 99, 141, 190, 232 and 337 of study.

Results:

In mice, oral administration of fenoldopam (dose range study) for 3 months produced chronic nephritis (in over 50% of mice) and purulent casts in the tubules of animals treated with 75 mg/kg/day and above. Chronic nephritis was described as showing destruction of tubular epithelium with regeneration of these cells. Purulents casts (presumably due to crystals) were composed of necrotic tubular epithelial cells and neutrophils. No evidence of renal damage or death was seen at 50 mg fenoldopam/kg/day and below; thus this dose was considered the maximum tolerated dose. Crystalluria (identified as the 7-beta-glucuronide conjugate of the drug) was noted at 25 mg/kg/day and above. Reduction of body weight (at 100 mg/kg and above in females and 50 mg/kg/day and above in males) was associated with reduced food consumption. Treatment-related mortality (mainly due to chronic nephritis) was noted in mice given 100 mg/kg/day and above; at 75 mg/kg/day and below a few accidental deaths occurred.

Fenoldopam, administered intravenously for about 2 weeks at doses ranging from 2 to 20 mg/kg/day, produced vasodilation in all drug treated rats; transient (20-30 min) muscular hypotonia was noted in the males at the 8 and 20 mg/kg doses.

In rat, i.v. infusion of fenoldopam for 24 hours produced intramedial necrosis and hemorrhage in large arterial branches of the splanchnic and renal vascular beds. The extent and severity of these lesions were dose-related and occurred with doses of 1-100 ug/kg/min but were not present at a dose of 0.1 ug/kg/min. Damage to endothelial cells was noted in gastric serosal arteries of 3 high-dose rats in which medial necrosis and hemorrhage were advanced.

In a 3-month oral (by gavage) toxicity study in rat, twice daily doses of fenoldopam (25, 50 or 100 mg/kg/day) produced salivation and irritability. On day 22 of the study, the high-dose was increased to 130 mg/kg/day but severe toxicity occurred (body weight loss, post-dosing abdominal spasms, decreased spontaneous activity, emaciation including deaths in 2 males and 2 females). Thus, the dosing was stopped for one day (day 35) and re-introduced as 75 mg/kg/day on from day 36 to 39, stopped again from days 40-42 and re-introduced as 60 mg/kg/day (days 43-49) and subsequently increased as shown on the dosing schedule above. As a precautionary measure, the low and mid doses were reduced (day 35) to 15 and 30 mg/kg/day, respectively. Overt toxic effects in the high dose animals failed to persist and over time the doses were increased to 25, 50 or 115 mg/kg/day. It appeared that the threshold doses for decreased body weight gain were between 115-130 mg/kg/day for females and 100-115 mg/kg/day for males. Hematologic findings included slight neutrophilia in males at the 1- and 3-month intervals (when the high-dose was 75 mg/kg/day). Crystals (identified as a beta-glucuronide conjugate at the 7-position of fenoldopam) were observed in the urine of some mid and high dose rats, from month 1 and week 1, respectively. Crystalluria in these rats often coincided with elevations in serum BUN, creatinine and WBC counts. These later changes correlated with renal damage. The high dose animals had histologic renal tubular damage (affecting 50 to 70% of the renal tissue) consisting of epithelial cell debris, polymorphonuclear leukocytes in lumen of cortical and medullary tubules, tubular dilatation showing evidence of epithelial regeneration, and early fibrosis. Eosinophilic crystalline deposits were often seen embedded in necrotic debris in both cortical tubules and collecting ducts. Similar pathologic changes involving 10% or less of kidney tissue were seen in some mid-dose rats (4 M and 3 F) but no crystalline deposits were seen either in their cortical or medullary tubules. No drug-induced renal damage was observed in the low-dose rats.

In dog, i.v. infusion with fenoldopam for 6 or 24 hours and for 6 hours per day for 14 days induced restlessness, salivation, emesis, ptosis and mydriasis but no arterial lesions comparable to those produced in the rat. Comparable (6 or 12 hour) i.v. infusion studies in (1 M, 1 F) dog were performed with dopamine. In the 6-hour study, 50 mcg dopamine/kg/min and above caused progressive and ultimately massive increases in MABP (attributable to peripheral vasoconstriction) and several types of ECG changes (indicative of myocardial electrophysiologic disturbance) progressing to severe arrhythmias at 100 mcg/kg/min. The cardiovascular system was clearly the principal target of toxicity produced by the 6-hr infusion of dopamine. In both dogs, medial necrosis and hemorrhage were seen affecting arteries and arterioles of virtually every tissue examined microscopically. In general, vessels most severely and frequently affected were the smaller caliber peripheral arteries (whose media comprised 3 to 4 layers of smooth muscle) and arterioles.

3. Tabulation of Carcinogenicity Studies

| Species | Strain | No./Group | Mode of Administration | Doses | Study Duration |
|---|---|---|---|---|---|
| Mouse | CR CD1 | 100M, 100F | Oral Gavage | 12.5, 25, 50-35 mg/kg/day | 24 months[4] |
| Rat | CR CD | 40M, 40F | Oral Gavage | 25-35 mg/kg/day | 18 months |
| Rat | CR CD | 100M, 100F | Oral Gavage | 5, 10-15, 20-25 mg/kg/day | 2 years |
| Rat | CR CD | 15M, 15F | Oral Gavage | 20 mg/kg/day | 1 year[2]<br>1 year[3] |

Notes: 1)
2) Interim report of clinical and physical signs - 12 months dosing of the 2-year carcinogenicity study in rats.
3) Renal monitoring study - separate but parallel to the 2-year carcinogenicity study in rats.

It must be noted that of the 3 carcinogenicity studies reported in this NDA, the mouse 2-year carcinogenicity study had not been previously evaluated. Although the rat 18-month (only portions of the data were previously submitted) and 2-year studies had been previously summarized/evaluated in the original IND pharmacology reviews for fenoldopam injectable these lack an FDA statistical review which is the current CDER practice.

Sponsor's summary of their (single treatment group) 18-month rat study is presented below.

| Doses* | Observations** |
|---|---|
| 25-35 mg/kg/day | Doses were increased from 25 to 35 mg/kg/day on Day 281. (Results of the 1-year oral study in rats revealed nephropathy at 40 mg/kg/day without an effect on survival).<br>No drug-related effect on body weight or mortality was observed. There was no effect on either the incidence or type of neoplasms observed. Chronic nephritis (cortical tubular nephropathy, inflammation, fibrosis and associated changes) was observed in the male and female drug-treated animals. In the drug-treated males, the incidence of periarteritis in pancreatic and splanchnic vascular beds was increased. However, its relationship to drug-treatment was uncertain due to the small sample size and the progressive nature of the lesion in aged rats. |

*Doses were divided b.i.d.
**No hematologic or clinical chemistry tests were performed.

This study (May '79 to Nov. '82) was designed to determine the potential of fenoldopam to cause hepatic neoplasia, because another structurally related chemical compound (unnamed in the NDA) at another pharmaceutical company had been found to be a hepatocarcinogen. A definitive 2-yr carcinogenicity study with fenoldopam was started Dec. 1981.

I have prepared reviews/evaluations of the 2-year mouse/rat carcinogenicity studies following the current toxicology review format in preparation for the FDA statistical review.

24-Month Oral Carcinogenicity Study in Mice (with an auxiliary group to monitor renal toxicity at 6 month interim sacrifice).

Testing Facility: -

Study Number: Study #006-007

Study Dates: April 7, 1982 to April 2-6, 1984

GLP Compliance: Yes.

Animals: Charles River CD-1 mice, both sexes, age about five weeks with a mean body weight of about 29 g for the males and 23 g for the females at initiation of study.

Mode of Administration of Fenoldopam: Solutions of fenoldopam in deionized water were prepared daily. Control and drug treated mice received 10 ml/kg deionized water or the drug solution, respectively, by gavage. The oral route of administration was chosen because it is one of the expected routes of administration in humans.

Dose levels: 100 M and 100 F mice per treatment group.

| | Group | Dose mg/kg/day[a] | Concentration mg/ml |
|---|---|---|---|
| I | Control | -- | -- |
| II | Control | -- | -- |
| III | Low-dose | 12.5 (16.42) | 1.64 |
| IV | Middle-dose | 25 (32.85) | 3.29 |
| V | High-dose | 50 -- 35 (65.70 -- 46.00)[b] | 6.57 -- 4.60 |
| VI | High-dose, Auxiliary | 50 (65.70) | 6.57 |

[a] Doses expressed as the base with the salt in parentheses.
[b] The dose was changed from 50 mg/kg/day to 35 mg/kg/day on day 209 of study.

Observations/Measurements: Mice were observed at least once daily for clinical effects and twice daily for mortality. They were examined monthly for tissue masses. Body weight and food consumption were recorded weekly through week 14, then every other week through week 43, and monthly thereafter. A necropsy was done on each mouse. Bones and tissues were examined macroscopically and microscopically. When appropriate, certain lesions were graded microscopically; both neoplastic and non-neoplastic data were statistically analyzed using Yate's corrected Chi-Square Test or Fisher's Exact Test.

Interim Sacrifice: No. Ten males and 10 females at 50 mg/kg/day (auxiliary group) were sacrificed after 6 months of dosing to monitor renal toxicity. In females, 8 of the 10 had slight or moderate chronic bilateral nephritis and three of these had renal cortex mineralization. In the males, two of 10 had slight chronic unilateral or subacute bilateral focal nephritis, respectively, and 1 of 10 had dilated renal pelvis.

Five females from the control group were sacrificed (day 199); none showed chronic nephritis or mineralization in the renal cortex; 2 showed minimal subacute focal unilateral nephritis. Thus, the high incidence of chronic nephritis in the drug treated females (50 mg/kg/day) appeared to be drug-related. On this basis, sponsor decreased the high-dose of the mouse carcinogenicity study to 35 mg/kg/day on day 209.

Mortality: Sponsor stated that no drug-related effect on mortality was apparent. The number of mice/group which survived to the end of the study were comparable.

Drug Associated Findings: A higher incidence of chronic nephritis was observed in female mice at 25 and 50 mg/kg/day; chronic nephritis was not seen at 12.5 mg/kg. The incidence and severity of chronic nephritis in all mice is presented below in Table 1, provided by sponsor.

— 24-Month Carcinogenicity Study of in CD-1 Mice

Incidence of Mice with Chronic Nephritis by Sex, Test Group and Degree of Severity

Table 1

Study #006-007

Found Dead or Killed Moribund

| Group | MALES | | | | | FEMALES | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | I | II | III | IV | V | I | II | III | IV | V |
| # Examined | 38 | 39 | 37 | 37 | 49 | 50 | 51 | 43 | 50 | 55 |
| Severity | | | | | | | | | | |
| 1 | 2 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 2 |
| 2 | 3 | 4 | 2 | 1 | 4 | 3 | 3 | 1 | 4 | 6 |
| 3 | 1 | 0 | 0 | 1 | 1 | 2 | 0 | 1 | 1 | 14 |
| 4 | 1 | 1 | 0 | 0 | 1 | 2 | 0 | 1 | 0 | 3 |
| 5 | 2 | 4 | 1 | 1 | 1 | 3 | 3 | 0 | 4 | 7 |
| Total | 9 | 10 | 4 | 4 | 8 | 10 | 7 | 4 | 10 | 32** I & II |

Killed Terminally

| Group | MALES | | | FEMALES | | | | |
|---|---|---|---|---|---|---|---|---|
| | I | II | V | I | II | III | IV | V |
| # Examined | 62 | 61 | 51 | 45 | 49 | 57 | 45 | 45 |
| Severity | | | | | | | | |
| 1 | 20 | 16 | 10 | 8 | 5 | 15 | 12 | 1 |
| 2 | 18 | 25 | 16 | 9 | 10 | 4 | 9 | 8 |
| 3 | 4 | 0 | 9 | 1 | 4 | 0 | 4 | 26 |
| 4 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 9 |
| 5 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Total | 43 | 42 | 35 | 18 | 19 | 19 | 26 | 44** I & II |

All Mice

| Group | MALES | | | FEMALES | | | | |
|---|---|---|---|---|---|---|---|---|
| | I | II | V | I | II | III | IV | V |
| # Examined | 100 | 100 | 100 | 95 | 100 | 100 | 95 | 100 |
| Severity | | | | | | | | |
| 1 | 22 | 17 | 11 | 8 | 6 | 16 | 13 | 3 |
| 2 | 21 | 29 | 20 | 12 | 13 | 5 | 13 | 16 |
| 3 | 5 | 0 | 10 | 3 | 4 | 1 | 5 | 40 |
| 4 | 2 | 2 | 1 | 2 | 0 | 1 | 0 | 12 |
| 5 | 2 | 4 | 1 | 3 | 3 | 0 | 5 | 7 |
| Total | 52 | 52 | 43 | 28 | 26 | 23 | 36 | 76** I & II |

**I & II $p \leq 0.01$ when compared to Control Groups I & II

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Another remarkable non-neoplastic lesion was a fibro-osseous lesion of the sternum in both control and drug-treated female mice. Incidence and severity of these lesions were greatest in females of the highest dosage group (see Table 2 below, provided by sponsor).

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Table 2 - 24-Month Carcinogenicity Study of in CD-1 Mice
Incidence of Fibro-osseous lesion of the Sternum in Female Mice by Test Group and Degree of Severity[a]

Study #006-007

**Found Dead or Killed Moribund**

| | FEMALES | | | | |
|---|---|---|---|---|---|
| Group | I | II | III | IV | V |
| # Examined | 50 | 51 | 43 | 50 | 55 |
| **Severity** | | | | | |
| 1 | 1 | 4 | 0 | 5 | 6 |
| 2 | 1 | 1 | 2 | 2 | 4 |
| 3 | 1 | 0 | 0 | 0 | 2 |
| 4 | 0 | 0 | 0 | 0 | 0 |
| 5 | 0 | 0 | 0 | 0 | 0 |
| Total | 3 | 5 | 2 | 7 | 12$^{**}$ |

**Killed Terminally**

| | FEMALES | | | | |
|---|---|---|---|---|---|
| Group | I | II | III | IV | V |
| # Examined | 45 | 49 | 57 | 45 | 45 |
| **Severity** | | | | | |
| 1 | 12 | 5 | 5$^{*I}$ | 5 | 11 |
| 2 | 4 | 6 | 6 | 7 | 12$^{*I}$ |
| 3 | 1 | 3 | 0 | 2 | 1 |
| 4 | 0 | 0 | 0 | 1 | 1 |
| 5 | 0 | 0 | 0 | 0 | 1 |
| Total | 17 | 14 | 11 | 15 | 26$^{**II}$ |

**All Mice (Groups I-V)**

| | FEMALES | | | | |
|---|---|---|---|---|---|
| Group | I | II | III | IV | V |
| # Examined | 95 | 100 | 100 | 95 | 100 |
| **Severity** | | | | | |
| 1 | 13 | 9 | 5 | 10 | 17 |
| 2 | 5 | 7 | 8 | 9 | 16$^{*I}$ |
| 3 | 2 | 3 | 0 | 2 | 3 |
| 4 | 0 | 0 | 0 | 1 | 1 |
| 5 | 0 | 0 | 0 | 0 | 1 |
| Total | 20 | 19 | 13 | 22 | 38$^{*I}$, $^{**II}$ |

[a] These data are derived from a semi-quantitative assessment and therefore do not correspond to incidences in Tables 9 and 10.

$^{*I}$ $p \leq 0.05$ when compared to Control Group I
$^{**II}$ $p \leq 0.01$ when compared to Control Group II

The probability of a relationship between chronic nephritis and fibro-osseous lesions of the sternum in high-dose females was considered. The data were analyzed statistically and sponsor reports that no correlation was found.

Regarding neoplastic findings in this study, the types of neoplasms found were said to commonly occur in CD-1 mice (the most common being neoplasms of lymphatic system, liver, lungs and glandular stomach). There was no statistically significant increase in incidence for any of these neoplasms. (Following are pertinent portions of tables provided by sponsor on incidences of each type of neoplastic lesion by sex and site.)

24-Month Carcinogenicity Study of in CD-1 Mice
Incidence of Each Type of Neoplastic Lesion by Sex and Test Group
All Mice (Groups I, II, and V)

Study #006-007

| Group | MALES | | | FEMALES | | |
|---|---|---|---|---|---|---|
| | I | II | V | I | II | V |
| SKIN # Examined | 100 | 100 | 100 | 95 | 100 | 100 |
| Fibrosarcoma of skin and subcutis | 0 | 0 | 0 | 0 | 0 | 1 |
| Squamous cell carcinoma | 0 | 0 | 0 | 0 | 0 | 1 |
| Malignant lymphoma | 0 | 3 | 1 | 3 | 3 | 5 |
| Fibrosarcoma - metastatic | 0 | 0 | 0 | 1 | 0 | 0 |
| MAMMARY GLAND # Examined | 26 | 28 | 28 | 94 | 98 | 97 |
| Adenocarcinoma | 0 | 1 | 0 | 4 | 4 | 4 |
| Malignant lymphoma | 0 | 2 | 1 | 3 | 7 | 5 |
| BONE MARROW SMEAR # Examined | 99 | 100 | 100 | 95 | 100 | 99 |
| Myelogenous leukemia | 1 | 0 | 0 | 0 | 0 | 0 |
| Malignant lymphoma | 2 | 4 | 3 | 3 | 4 | 6 |
| Malignant myeloma | 0 | 0 | 1 | 0 | 0 | 0 |
| BLOOD SMEAR # Examined | 65 | 63 | 52 | 47 | 50 | 49 |
| Monocytic leukemia | 0 | 0 | 0 | 1 | 0 | 0 |
| Myelogenous leukemia | 0 | 0 | 1 | 0 | 0 | 0 |
| LYMPH NODES | | | | | | |
| Malignant lymphoma | 6 | 5 | 7 | 8 | 16 | 12 |
| Malignant myeloma | 0 | 0 | 1 | 0 | 0 | 0 |
| Malignant histiocytoma, fibrous | 1 | 1 | 0 | 2 | 0 | 1 |
| Adenocarcinoma of infraorbital lacrimal gland - metastatic | 1 | 0 | 0 | 0 | 0 | 0 |
| Adenocarcinoma of lungs - metastatic | 1 | 0 | 0 | 0 | 0 | 0 |
| Endometrial stromal sarcoma - metastatic | — | — | — | 1 | 0 | 0 |
| Mesenteric Lymph Nodes | | | | | | |
| Malignant lymphoma | 3 | 3 | 4 | 7 | 9 | 5 |
| Malignant histiocytoma, fibrous | 0 | 0 | 0 | 0 | 0 | 1 |
| Fibrosarcoma - metastatic | 0 | 0 | 0 | 1 | 0 | 1 |
| Hemangiosarcoma | 0 | 0 | 0 | 1 | 0 | 0 |
| Adenocarcinoma of uterus - metastatic | — | — | — | 0 | 0 | 1 |
| MANDIBULAR LYMPH NODES # Examined | 99 | 100 | 100 | 94 | 100 | 99 |
| Malignant lymphoma | 9 | 9 | 10 | 12 | 16 | 14 |
| Malignant myeloma | 0 | 0 | 1 | 0 | 0 | 0 |
| Malignant histiocytoma, fibrous | 1 | 1 | 0 | 1 | 0 | 1 |
| Reticulum cell sarcoma | 0 | 0 | 0 | 1 | 0 | 0 |
| Adenocarcinoma of lungs - metastatic | 1 | 0 | 0 | 0 | 0 | 0 |

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24-Month Carcinogenicity Study of in CD-1 Mice
Incidence of Each Type of Neoplastic Lesion by Sex and Test Group
All Mice (Groups I, II, and V) (Cont'd)

Study #006-007

| Group | MALES I | MALES II | MALES V | FEMALES I | FEMALES II | FEMALES V |
|---|---|---|---|---|---|---|
| HEART # Examined | 100 | 100 | 100 | 95 | 100 | 100 |
| Malignant lymphoma | 1 | 2 | 2 | 2 | 4 | 6 |
| Malignant histiocytoma, fibrous | 0 | 0 | 0 | 1 | 0 | 0 |
| Rhabdomyosarcoma of auricle | 0 | 0 | 1 | 0 | 0 | 0 |
| AORTA # Examined | 100 | 99 | 100 | 93 | 98 | 98 |
| Malignant lymphoma | 1 | 2 | 0 | 2 | 0 | 2 |
| Tumor embolus | 0 | 0 | 0 | 1 | 0 | 0 |
| LUNGS WITH BRONCHI # Examined | 100 | 100 | 100 | 95 | 100 | 100 |
| Adenoma | 20 | 16 | 19 | 10 | 10 | 14 |
| Adenocarcinoma | 5 | 10 | 5 | 3 | 4 | 4 |
| Malignant lymphoma | 5 | 8 | 10 | 11 | 18 | 14 |
| Malignant myeloma | 0 | 0 | 2 | 0 | 0 | 0 |
| Malignant histiocytoma, fibrous | 0 | 0 | 0 | 1 | 0 | 0 |
| Reticulum cell sarcoma | 0 | 0 | 0 | 1 | 0 | 0 |
| Adenocarcinoma of mammary gland - metastatic | 0 | 0 | 0 | 1 | 0 | 1 |
| Fibrosarcoma - metastatic | 0 | 0 | 0 | 0 | 0 | 1 |
| Osteosarcoma - extraskeletal | 0 | 0 | 0 | 0 | 0 | 1 |
| TRACHEA # Examined | 100 | 100 | 100 | 95 | 100 | 100 |
| Malignant lymphoma | 0 | 2 | 2 | 0 | 1 | 1 |
| ESOPHAGUS # Examined | 100 | 100 | 100 | 95 | 100 | 100 |
| Malignant lymphoma | 0 | 0 | 0 | 0 | 1 | 0 |
| STOMACH - Cardiac # Examined | 100 | 100 | 100 | 95 | 100 | 100 |
| Adenoma | 6 | 3 | 3 | 1 | 0 | 0 |
| Adenocarcinoma | 6 | 3 | 2 | 1 | 1 | 0 |
| Malignant lymphoma | 2 | 5 | 4 | 5 | 6 | 4 |
| Malignant lymphoma of esophageal part | 0 | 0 | 0 | 0 | 0 | 1 |
| Fibrosarcoma - metastatic | 0 | 0 | 0 | 0 | 0 | 1 |
| STOMACH - Fundic # Examined | 100 | 100 | 100 | 95 | 100 | 100 |
| Adenoma | 2 | 5 | 1 | 2 | 4 | 0 |
| Adenocarcinoma | 5 | 6 | 4 | 6 | 1 | 0 |
| Malignant lymphoma | 1 | 2 | 2 | 5 | 5 | 1 |
| Fibrosarcoma - metastatic | 0 | 0 | 0 | 0 | 0 | 1 |
| Osteosarcoma - extraskeletal | 0 | 0 | 0 | 0 | 0 | 1 |
| STOMACH - Pyloric # Examined | 100 | 100 | 100 | 95 | 100 | 100 |
| Adenoma | 3 | 0 | 1 | 0 | 0 | 1 |
| Adenocarcinoma | 3 | 2 | 3 | 2 | 0 | 0 |
| Malignant lymphoma | 2 | 2 | 2 | 4 | 5 | 1 |
| Adenocarcinoma of uterus - metastatic | — | — | — | 0 | 0 | 1 |
| Fibrosarcoma - metastatic | 0 | 0 | 0 | 0 | 0 | 1 |
| Leiomyosarcoma of uterus - metastatic | — | — | — | 0 | 1 | 0 |

24-Month Carcinogenicity Study of .in CD-1 Mice
Incidence of Each Type of Neoplastic Lesion by Sex and Test Group
All Mice (Groups I, II, and V) (cont'd)

Study #006-007

| Group | MALES | | | FEMALES | | |
|---|---|---|---|---|---|---|
| LIVER # Examined | I | II | V | I | II | V |
| | 100 | 100 | 100 | 95 | 100 | 100 |
| Adenoma of hepatocytes | 15 | 12 | 17 | 1 | 4 | 2 |
| Adenocarcinoma of hepatocytes | 13 | 13 | 11 | 0 | 0 | 0 |
| Hemangioma | 1 | 0 | 2 | 0 | 0 | 0 |
| Malignant lymphoma | 7 | 8 | 11 | 10 | 18 | 10 |
| Malignant myeloma | 1 | 0 | 2 | 0 | 0 | 0 |
| Malignant histiocytoma, fibrous | 0 | 0 | 0 | 3 | 0 | 2 |
| Reticulum cell sarcoma | 0 | 0 | 0 | 1 | 0 | 0 |
| Endometrial stromal sarcoma - metastatic | — | — | — | 0 | 2 | 0 |
| Hemangiosarcoma - metastatic | 0 | 0 | 1 | 0 | 0 | 0 |
| Leiomyosarcoma of uterus - metastatic | — | — | — | 1 | 1 | 0 |
| GALL BLADDER # Examined | 98 | 96 | 100 | 94 | 99 | 99 |
| Malignant lymphoma | 4 | 3 | 2 | 1 | 5 | 4 |
| Malignant myeloma | 0 | 0 | 1 | 0 | 0 | 0 |
| Malignant histiocytoma, fibrous | 0 | 0 | 0 | 1 | 0 | 0 |
| KIDNEYS # Examined | 100 | 100 | 100 | 95 | 100 | 100 |
| Adenoma | 1 | 1 | 1 | 0 | 0 | 0 |
| Adenocarcinoma | 1 | 0 | 1 | 0 | 0 | 0 |
| Malignant lymphoma | 8 | 9 | 14 | 12 | 20 | 14 |
| Malignant myeloma | 0 | 0 | 2 | 0 | 0 | 0 |
| Malignant histiocytoma, fibrous | 0 | 0 | 0 | 1 | 0 | 0 |
| Endometrial stromal sarcoma, unilateral - metastatic | — | — | — | 1 | 0 | 0 |
| ADRENALS # Examined | 100 | 100 | 95 | 95 | 100 | 100 |
| Adenoma of cortex | 0 | 1 | 0 | 0 | 0 | 0 |
| Adenoma of cortical spindle cells | 0 | 0 | 0 | 0 | 1 | 0 |
| Adenocarcinoma of cortical spindle cells | 0 | 0 | 0 | 1 | 0 | 1 |
| Pheochromocytoma | 0 | 0 | 0 | 3 | 0 | 0 |
| Malignant lymphoma | 0 | 1 | 2 | 3 | 6 | 5 |
| Malignant myeloma | 0 | 0 | 1 | 0 | 0 | 0 |
| Malignant histiocytoma, fibrous | 0 | 0 | 0 | 1 | 0 | 0 |
| Reticulum cell sarcoma | 0 | 0 | 0 | 1 | 0 | 0 |
| Fibrosarcoma - metastatic | 0 | 0 | 0 | 1 | 0 | 0 |

Oral administration of fenoldopam by gavage to Charles River CD-1 mice once daily for 24 months did not result in a higher incidence of neoplasia, degree of malignancy or multiplicity of neoplasms. See overall summary Table 3 below provided by sponsor.

Table 3

24-Month Carcinogenicity Study of in CD-1 Mice
Incidence of Mice With Neoplasms by Sex and Test Group
All Mice (Groups I, II, & V)

Study #006-007

| Group | MALES I | MALES II | MALES V | FEMALES I | FEMALES II | FEMALES V |
|---|---|---|---|---|---|---|
| Number of mice examined | 100 | 100 | 100 | 95 | 100 | 100 |
| Number of mice with neoplasms | 66 | 69 | 74 | 66(69)[a] | 70 | 60 |
| Number of mice with benign neoplasms | 41 | 39 | 41 | 32(34) | 33 | 24 |
| Number of mice with malignant neoplasms | 45 | 44 | 46 | 51(54) | 56 | 42 |
| Number of mice with multiple neoplasms | 30 | 26 | 26 | 26(27) | 30 | 16*[II] |

[a] Percent given in parenthesis.

*[II] $p \leq 0.05$ when compared to Control Group II

24-Month Oral Carcinogenicity Study in Rats (with a parallel study to monitor renal toxicity at 12 month sacrifice).

Testing Facility:

Study Number(s): Report Nos. TP013VD and VD 4403 (Renal monitoring study).

Study Dates: December 2, 1981 (1st day of dosing) to December 5-9, 1983 (necropsy dates).

GLP Compliance: Yes

Animals: Charles River CD (Sprague-Dawley derived) albino rats, both sexes, age about 7 weeks with an average body weight of about 252 g for males and 183 g for females at initiation of study.

Mode of Administration of Test Agent: Solutions of fenoldopam in distilled water were prepared daily. Two control and three drug treated groups of rats received 10 ml/kg distilled water or the drug solution once daily, 7 days a week by gavage. The oral route of administration was chosen because it is one of the expected routes of administration in humans.

Dose Levels:

| Group | No. of Rats Male | No. of Rats Female | Dosage* mg/kg | Days of Treatment** |
|---|---|---|---|---|
| Control I | 100 | 100 | Distilled Water | 1-733/737 |
| Control II | 100 | 100 | Distilled Water | 1-733/737 |
| Low Dose | 100 | 100 | 5 (6.57) | 1-733/737 |
| Mid Dose | 100 | 100 | 10 (13.14) | 1-371 |
| | | | 15 (19.71) | 372-733/737 |
| High Dose | 100 | 100 | 20 (26.28) | 1-371 |
| | | | 25 (32.85) | 372-733/737 |

* The dosage of is stated as the base with the methanesulfonate in parentheses.

** Based on the microscopic examination of kidneys of rats (at 11 months) from the "renal monitoring study", the doses of fenoldopam were raised from 10 to 15 mg/kg/day and from 20 to 25 for the mid and high dose groups, respectively, from day 372 for the remainder of the study.

The purpose of the "renal monitoring study" was to assess the extent and progress of renal damage caused by fenoldopam during the course of the study and to determine whether the dose in the 2-year rat carcinogenicty study should be adjusted in the event that survival of the animals might be jeopardized. This study was conducted in parallel with the 2-year rat carcinogenicity study and the one dose of fenoldopam was set to coincide with the high dose administered to rats in the 2-year carcinogenicity experiment.

The one drug-treated group (25 males and 25 females) in the "renal monitoring study" was dosed initially with 20 mg fenoldopam/kg once daily and the controls (15 males and 15 females) were treated with distilled water. Body weights were recorded at least once prior to the start of drug treatment and weekly during the dosing period. Urine samples from 10 rats/sex/group were examined prior to the start and at every 3 months. At about 11 months (day 348), 5 rats/sex from the control group and 10 rats/sex from the drug-treated group were killed and their kidneys were examined microscopically. Based on the microscopic evaluation of the drug treated rats, the dose was raised from 20 to 25 mg/kg/day. After 18 months of dosing all the remaining rats were killed and their kidneys were also examined microscopically.

Observations/Measurements: Rats in the 24-month carcinogenicity study were subjected to the following in-life observations at the indicated intervals.

| | Pre-drug | During Drug Treatment |
|---|---|---|
| Body Weights | 2X | Weekly during the first 6 months and every 2 weeks thereafter. |
| Food Consumption (7-day) | 1X | Weekly during the first 6 months; every 4 weeks for the next 6 months; and at the 18- and 24-month intervals. |
| Physical Examination (time of onset, location, size and growth characteristics of masses noted) | 1X | Monthly |
| Clinical Ophthalmology | 1X | Prior to autopsy on days 734-738 |

No hematologic or clinical tests were required in the protocol.

The rats were observed daily after dosing for clinical signs. Rats found dead or those killed moribund during study were autopsied and their tissues examined grossly and processed for histopathology.

Blood smears were prepared and stained from all rats at necropsy except those found dead during the study.

The following tissues from all control and high dose rats, and all rats of the low and middle dose groups which died or were killed moribund during the study, were examined microscopically: all gross lesions, tissue masses, submandibular lymph nodes, mammary gland, kidneys, urinary bladder, testes, salivary gland, sternebrae or femur and bone marrow, thymus, trachea, lungs and mainstrem bronchi, heart, thyroids (parathyroids when included in section of thyroid), liver, pancreas, spleen, mesenteric lymph node, adrenals, prostate, ovaries (plus mesovarium), uterus, brain (three sections including frontal cortex and basal ganglia, parietal cortex and thalamus, and cerebellum and pons), pituitary, eye (if grossly abnormal), esophagus, stomach, small intestine (duodenum, jejunum, ileum) and colon.

Initially, only tissue masses and gross lesions from low and middle dose rats killed at the end-of-study autopsy were examined microscopically. Subsequently, as per protocol amendment, the kidneys, pancreas, testes, stomach, lung, thyroid and adrenal glands from male and female rats of the low and middle dose groups which survived to the end of the study were examined microscopically so that a comprehensive evaluation of patholgical changes seen in these tissues could be made of all dose groups in the study.

Neoplastic/other data were statistically analyzed using various methods fully described in the NDA.

Interim Sacrifice: No.

Mortality: There were no statistically significant survival differences between drug-treated and control groups. Survival curves for all groups were analyzed using Kaplan-Meier estimates and survival differences were tested using the Wilcoxon Rank test. The weekly mortality for males and females and the cumulative mortality at weekly intervals was similar in the drug-treated and control groups. The overall percent mortality by the end of the study (week 106) was as follows:

| Group | Females (n = 100) | Males (n = 100) |
|---|---|---|
| Control I | 72% | 69% |
| Control II | 74% | 68% |
| Low dose | 68% | 72% |
| Mid dose | 74% | 64% |
| High dose | 77% | 76% |

Findings:

There were no significant survival differences among the treated groups for either sex.

The neoplastic lesions were analyzed on the basis of incidences using Fisher's exact test. The following tumor incidence tables were provided by the sponsor.

The reported incidences of tumors in control and treated rats are presented in summary Tables 4 through 6 provided by sponsor. Overall, sponsor reports that drug treated groups showed no significant increases in the numbers of rats with neoplasms compared to controls (Table 4).

Table 4

2-Year Carcinogenicity Study in Rats
(Penaidepam)
Incidence of Neoplasms
All Animals

MALES

| Group | I | II | III* | IV* | V |
|---|---|---|---|---|---|
| Number of rats examined | 100 | 100 | 100 | 100 | 100 |
| Number of rats with neoplasms | 78 | 79 | 88 | 81 | 86 |
| Number of rats with benign neoplasms | 69 | 68 | 82 | 68 | 79 |
| Number of rats with malignant neoplasms | 26 | 29 | 30 | 38 | 29 |

FEMALES

| Group | I | II | III* | IV* | V |
|---|---|---|---|---|---|
| Number of rats examined | 100 | 100 | 100 | 100 | 99 |
| Number of rats with neoplasms | 92 | 95 | 89 | 93 | 94 |
| Number of rats with benign neoplasms | 86 | 89 | 88 | 92 | 89 |
| Number of rats with malignant neoplasms | 33 | 36 | 26 | 33 | 38 |

* Only gross lesions and tissues listed in Protocol Amendment IX were examined microscopically in rats of the low (III) and middle (IV) dose groups killed terminally at the end-of-study necropsy. (Table provided by sponsor)

Regarding the animals found dead/moribund killed (FD/MK) during the study, the number of male rats with neoplasms (malignant and/or benign) and the number of male rats with benign neoplasms were significantly increased at the high dose when compared to control Group I but not to control Group II.

Table 5

2-Year Carcinogenicity Study in Rats
(ERNOLDOPAM)
Incidence of Neoplasms
Found Dead/Moribund Killed Animals

MALES

| Group | I | II | III* | IV* | V |
|---|---|---|---|---|---|
| Number of rats examined | 67 | 66 | 69 | 64 | 76 |
| Number of rats with neoplasms | 49(73)** | 51(77) | 61(88) | 51(80) | 66(87)[a] |
| Number of rats with benign neoplasms | 41(61) | 43(65) | 57(83) | 42(66) | 59(78)[b] |
| Number of rats with malignant neoplasms | 18(27) | 21(32) | 21(30) | 24(38) | 22(29) |

FEMALES

| Group | I | II | III* | IV* | V |
|---|---|---|---|---|---|
| Number of rats examined | 72 | 74 | 68 | 73 | 76 |
| Number of rats with neoplasms | 65(90)** | 70(95) | 58(85) | 66(90) | 71(93) |
| Number of rats with benign neoplasms | 60(83) | 64(86) | 57(84) | 65(89) | 66(87) |
| Number of rats with malignant neoplasms | 21(29) | 24(32) | 18(26) | 26(36) | 30(39) |

* All tissues of rats in the low (III) and middle (IV) dose groups, found dead or killed in a moribund state, were examined microscopically.
** Percent given in parenthesis.

[a] Comparison with Control I in Fisher's exact test is statistically significant ($p = 0.032$)
[b] Comparison with Control I in Fisher's exact test is statistically significant ($p = 0.025$)

As presented below in Table 6 there was no evidence of a drug-related effect on tumor incidence in rats terminally killed (TK).

Table 6

Fenoldopam

2-Year Carcinogenicity Study in Rats

Incidence of Neoplasms
Terminal Killed Animals

MALES

| Group | I | II | III* | IV* | V |
|---|---|---|---|---|---|
| Number of rats examined | 33 | 34 | 31 | 36 | 24 |
| Number of rats with neoplasms | 29(88)** | 28(82) | 27(87) | 30(83) | 20(83) |
| Number of rats with benign neoplasms | 28(85) | 25(74) | 25(81) | 26(72) | 20(83) |
| Number of rats with malignant neoplasms | 8(24) | 8(24) | 9(29) | 14(39) | 7(29) |

FEMALES

| Group | I | II | III* | IV* | V |
|---|---|---|---|---|---|
| Number of rats examined | 28 | 26 | 32 | 27 | 23 |
| Number of rats with neoplasms | 27(96)** | 25(96) | 31(97) | 27(100) | 23(100) |
| Number of rats with benign neoplasms | 26(93) | 25(96) | 31(97) | 27(100) | 23(100) |
| Number of rats with malignant neoplasms | 12(43) | 12(46) | 8(25) | 7(26) | 8(35) |

* All tissues of rats in the low (III) and middle (IV) dose groups, found dead or killed in a moribund state, were examined microscopically.
** Percent given in parenthesis.
(Table prepared in Sponsor)

The only notable neoplastic findings reported were in mammary and pituitary glands of drug-treated females. Although not dose-related, TK drug-treated females showed an increase in the incidence of mammary gland fibroadenomas (low-dose- 87%, mid-dose- 100% and high-dose- 78%) compared to controls (Group I- 71% and Group II- 44%). Overall, the high-dose females (FD/MK plus TK) showed an incidence (54%) of mammary gland fibroadenoma that was statistically significant ($p = 0.04$) when compared to the incidence in females of control Group II(40%), but not control Group I (55%). It should be noted that the incidence of mammary gland fibroadenoma in high-dose females falls within the incidence range of the two concurrent control groups. The table below, provided by the sponsor, shows the incidences (FD/MK, TK and sum total) of mammary gland fibroadenomas in the female rats in this study.

**Incidence of Mammary Gland Fibroadenoma**

| Group | I | | II | | III | | IV | | V | |
|---|---|---|---|---|---|---|---|---|---|---|
| | M | F | M | F | M | F | M | F | M | F |
| FD/MK | 2/65 | 35/71 | 2/65 | 29/74 | 1/69 | 34/68 | 0/61 | 34/72 | 0/72 | 34/73 |
| TK | 0/33 | 20/28 | 1/34 | 11/25 | 0/1 | 21/24 | 0/0 | 18/18 | 0/24 | 18/23 |
| ALL | 2/98 | 55/99 | 3/99 | 40/99 | 1/70 | 55/92 | 0/61 | 52/100 | 0/96 | 52/96[b] |

[b] Comparison with control II is statistically significant ($p = 0.04$).

Historical control data for mammary fibroadenoma/adenoma and pituitary adenoma incidence in the Sprague-Dawley rat (2 yr studies) were submitted in NDA Amendment dated 12-29-89. The following table, prepared by sponsor, shows incidences of mammary fibroadenoma in females of 36% and 31%; these incidences are lower than those (71% and 78%) reported for either of the control groups in the fenoldopam carcinogenicity study. In a later NDA Amendment, dated 02-05-90, sponsor provided additional historical control data for one of the two 2-yr studies showing the incidence of mammary fibroadenoma in females rats found dead as 31% (incidence for high-dose fenoldopam was 46%) and in females TK as 40% (incidence for high-dose fenoldopam was 78%).

Incidence of Benign Mammary Tumors (Historical Control)

| | Males | | Females | |
|---|---|---|---|---|
| | Control I | Control II | Control I | Control II |
| Compound A | | | | |
| Fibroadenoma/adenoma | 2/80 (4%) | 0/77 (0%) | 37/80 (46%) | 35/80 (44%) |
| Compound B | | | | |
| Fibroadenoma | 0/57 (0%) | 0/57 (0%) | 26/72 (36%) | 23/75 (31%) |
| Adenoma | 0/57 (0%) | 1/57 (2%) | 6/72 ( 8%) | 13/75 (17%) |
| Fibroadenoma/adenoma | 0/57 (0%) | 1/57 (2%) | 32/72 (44%) | 36/75 (48%) |
| SK&F 82526-J | | | | |
| Fibroadenoma | 2/98 (4%) | 3/99 (3%) | 55/99 (56%) | 40/99 (40%) |
| Adenoma | 0/98 (0%) | 1/99 (1%) | 9/99 ( 9%) | 7/99 ( 7%) |
| Fibroadenoma/adenoma | 2/98 (4%) | 4/99 (4%) | 64/99 (65%) | 47/99 (47%) |

Regarding the incidence of pituitary adenoma (pars anterior), in high-dose female rats FD/KM (83%) this value achieved statistical significance (p= 0.03) when compared with the incidence (68%) in control females in Group I, but not Group II (77%). Similarly, the incidence (83%) of pituitary adenoma in all high dose females (FD/KM plus TK) was statistically significant (p= 0.03) when compared to the incidence (71%) in females in control Group I, but not Group II (78%).

Incidence of Pituitary Adenoma

| Group | I | | II | | III | | IV | | V | |
|---|---|---|---|---|---|---|---|---|---|---|
| | M | F | M | F | M | F | M | F | M | F |
| FD/MK* | 32/65 | 49/72 | 35/65 | 56/73 | 44/69 | 49/67 | 35/64 | 55/73 | 47/74 | 63/76[a] |
| TK** | 21/33 | 22/28 | 16/33 | 22/26 | 11/11 | 28/28 | 11/13 | 16/16 | 16/23 | 19/23 |
| ALL | 53/98 | 71/100 | 51/98 | 78/99 | 55/80 | 77/95 | 46/77 | 71/89 | 63/97 | 82/99[a] |

* FD/MK = Found Dead or Killed Moribund.
** TK = Terminal Killed.

[a] Comparison with control I is statistically significant (p = 0.03).

Historical control data for pituitary tumors (NDA Amendment dated 12-29-89) from two 2-year carcinogenicity studies in same strain of rat are presented below in table submitted by sponsor. The incidences for pituitary adenoma in four female control groups ranged from 75% up to 89%, which is consistent with the incidences (71% and 78%) reported for the two female control groups in the fenoldopam 2-year study.

Incidence of Pituitary Adenoma (Historical Control)

| | Males | | Females | |
|---|---|---|---|---|
| | Control I | Control II | Control I | Control II |
| Compound A | 49/77 (62%) | 43/79 (54%) | 60/80 (75%) | 69/78 (88%) |
| Compound B | 42/75 (56%) | 40/74 (54%) | 67/75 (89%) | 64/75 (85%) |
| SK&F 82526-J | 53/98 (54%) | 51/98 (52%) | 71/100 (71%) | 78/99 (78%) |

In a later NDA Amendment dated 02-05-90, sponsor provided additional historical control data for one (Compound B) of the two 2-yr studies. That data reported the incidences of pituitary adenomas in the two control female groups found dead as 65% and 87% and in those terminally killed as 84% and 85% (incidence for high dose females on fenoldopam was about 83% in each case).

Sponsor stated that results of the present study and historical control data suggest that "administration of fenoldopam had no biologically significant effect on the incidence of pituitary adenoma in high-dose female rats in this study."

Except for the equivocal increase in mammary gland fibroadenomas in the high-dose females FD/MK, the results of this study suggest that oral administration of fenoldopam to Sprague-Dawley, Charles River CD rats by gavage, once daily for 24 months (106 weeks) at dosages of 5, 15 or 25 mg/kg/day had no effect on the incidence of benign or malignant neoplasms.

Tumor incidence data from the 2 yr rat and mouse studies of fenoldopam were submitted, by sponsor, in computer readable format, to CDER's Division of Biometrics on July 17, 1990.

Non-neoplastic drug-associated findings in rats dosed with fenoldopam for up to 2 yrs were as follows:

There was a dose-related increase in the incidence and severity of renal pathology in mid- and high-dose male and female rats- hyperplasia/hypertrophy of collecting duct epithelium, inflammatory debris in collecting duct and hyperplasia/hypertrophy of pelvic epithelium at the tip of the renal papilla believed to be related to the 7-beta-glucuronide metabolite of fenoldopam.

Fenoldopam increased (p less than 0.05) the incidence of polyarteritis nodosa (pancreas, stomach and testes) in mid- and high dose male rats compared to male controls; an increase (p less than 0.05) in polyarteritis nodosa (pancreas and stomach) was seen in high dose females compared to female controls. This lesion is thought to result from pharmacologic activity of fenoldopam mediated via activation of the post-junctional dopaminergic $DA_1$ receptor. Sponsor asserts that the induction of polyarteritis nodosa in the rat is not an exclusive property of fenoldopam and that other drugs (i.e., caffeine and theophylline) are known to cause an increased incidence of polyarteritis in rats upon long-term oral administration.

Regarding the salient observations in the "renal monitoring study", the 5 rats/sex from the control group and 10 rats/sex from the fenoldopam (20 mg/kg/day) treated group sacrificed on day 348 (at about 11 months) showed spontaneous renal disease; this was slightly more severe in dosed male rats compared to controls. Although histopathology revealed drug-related sporadic, focal areas of renal tubular injury/regeneration in both kidneys of 8/10 male and 1/10 female fenoldopam treated rats, the damage was considered minor and involved less than 5-10% of kidney tissue. Five of the 8 males with renal lesions showed epithelial debris and/or pus cells in the lumen of renal tubules. One male rat showed crystalline material morphologically similar to glucuronide conjugate of fenoldopam in the renal tubules. Urinalysis (conducted on 10 M/F rats of both control/drug treated groups) revealed the presence of characteristic crystals of fenoldopam glucuronide at 3-month (1 F), 6-month (4F, 3M), and 9-month (6F, 5M) intervals. At day 348 (and for 6 months thereafter), the dose of fenoldopam was raised from 20 to 25 mg/kg/day. Administration of fenoldopam at the higher dose caused renal damage sufficient to cause death of 4 females between 12 and 18 months of treatment. Although urinalysis was positive for crystals (glucuronide of fenoldopam) in most rats at various intervals throughout the study, there was no clear correlation between crystalluria and renal damage. However, the majority of rats with positive urinary crystals, at one or more intervals, showed evidence of renal damage (focal, moderate or in one case severe).

Special Investigative Studies.

Because i.v. infusion of fenoldopam for 24 hours produced dose-related arterial lesions (intramedial necrosis and hemorrhage) in the splanchnic and renal vasculature of the rat but not in dog or monkey, the following studies were conducted to investigate the etiology and pathogenesis of arterial lesions induced by the drug.

Tabulation of Special Investigative Studies Provided by Sponsor in this NDA.

| Species | Strain | No./Group | Mode of Administration[B] | Doses | Study Duration* |
|---|---|---|---|---|---|
| Rat | CR CD** | 4M, 4F | I.V. Infusion | 100 mcg/kg/min | 24 hours |
| Rat | CR CD | 4M, 4F | I.V. Infusion | 100 mcg/kg/min for 1, 4 and 8 hours | 8 hours |
| Rat | CR CD | 4M, 4F | I.V. Infusion | 5, 100 mcg/kg/min in pgv*** ; 5, 100 mcg/kg/min in 0.9% saline | 24 hours |
| Rat | CR CD | 4M | I.V. Infusion | 5, 100 mcg/kg/min | 24 hours |
| Rat | CR CD | 6 or 12M | I.V. Infusion | 2 mcg/kg/min hydralazine HCl, 20 mcg/kg/min Na nitroprusside, 5,20,50 and 100 mcg/kg/min dopamine, 100 mcg/kg/min of each of the following: | 24 hours |
| Rat | CR CD | 5, 6 or 9M | I.V. Infusion | 50 mcg/kg/min of fenoldopam for 1 and 4 hours, 20 mcg/kg/min of dopamine for 1, 4, and 24 hours | 24 hours |
| Rat | CR CD | 3M | I.V. Infusion | 50 mcg/kg/min of fenoldopam for 4 and 24 hours, 20 mcg/kg/min of dopamine HCl for 4 and 24 hours | 24 hours |
| Rat | CR CD | 2 or 6M | I.V. Infusion | Each of the following alone and in combination with 50 mcg/kg/min of fenoldopam: 2 mcg/kg/min of hydralazine, 20 mcg/kg/min Na nitroprusside, 10 mg/kg phenoxybenzamine, subcutanously | 24 hours |
| Rat | CR CD | 18 or 20M | I.V. Infusion | 50 mcg/kg/min of fenoldopam, 20 mcg/kg/min of dopamine for 24 hours | 28 days |
| Rat | CR CD | 1-14M | I.V. Infusion | 20 mcg/kg/min propranolol, 10 mg/kg phenoxybenzamine s.c., 10 mcg/kg/min LY 53857(A), 10 mcg/kg/min l-sulpiride, 10 mcg/kg/min , 20 mcg/kg/min Na nitroprusside, 2 mcg/kg/min hydralzaine, 1. 50 mcg/kg/min fenoldopam, 100 mcg/kg/min 50 mcg/kg/min dopamine; all drugs alone and/or in combination with fenoldopam or dopamine for 24 hrs. | 24 hours |

* The study was terminated when all infusions were completed.
** CR CD = Charles River caesarean derived rats
*** pgv = propylene glycol vehicle
(A) Serotonergic receptor antagonist

(B) The rate of infusion in each of these studies was 0.005 ml/min. The vehicle, however, varied with the study (saline, propylene glycol or Water for Injection).

N.B. Regarding the infusion of fenoldopam in rats for up to 8 hrs, sponsor stated that although the drug induced smooth muscle necrosis of the media of small arteries (effect seen after 4 hrs of infusion) in certain abdominal organs supplied by the splanchnic arterial vasculature, the lesions were at very low incidence and frequency. Sponsor considered that detection of lesions at a frequency that would allow meaningful comparison with other drugs would probably require infusion of the drug for at least 16 hrs.

Summary Table of Drug-Related Observations in Special Investigative Studies.
(Provided by sponsor).

| Species | Duration of study | Doses | Observations |
|---|---|---|---|
| Rat | 24 hours | 100 mcg/kg/min | To determine the effect of i.v. infusion of fenoldopam on unrestrained rats. Smooth muscle necrosis and intramedial hemorrhage in splanchnic (stomach, intestines, ovaries, pancreas) and renal arteries were seen in all animals on study. Arterial lesions produced in unrestrained rats were identical to those seen in restrained rats in previous studies. [Ref. VD 4203] |
| Rat | 24 hours | 100 mcg/kg/min for 1, 4 and 8 hours | To determine the effect of the duration of fenoldopam infusion on the development of arterial lesions. Small arterial lesions were observed in 1 male and 1 female rat (2/8 rats) infused for 4 hours and 1 female (1/8 rats) infused for 8 hours. The low incidence and frequency of these findings did not permit a meaningful determination of the effect of infusion duration. [Ref. VD 4204] |
| Rat | 24 hours | 5, 100 mcg/kg/min in pgv**<br>5, 100 mcg/kg/min in 0.9% saline | To determine the effect of certain procedures (type of vehicle, warming of the tail prior to blood collection, time of death following infusion, method of exsanguination) on the reproducibility of the arterial lesions during i.v. infusion. The arterial lesion was reproduced at both 5 and 100 mcg/kg/min with both vehicles. However, the incidence was greater at the higher dosage. The variables tested had no apparent effect on the etiology of the arterial lesion. [Ref. VD 4205] |
| Rat | 24 hours | 5, 100 mcg/kg/min | To examine the ultrastructure of the arterial lesion and to investigate its pathogenesis. Medial smooth muscle cells were the principal target of drug-induced toxicity. Alterations in endothelial cells may occur only secondarily to damage to medial smooth muscle cells. Connective tissue components of the arterial wall were not a primary target of toxicity. Red blood cells appeared to escape from the arterial lumen into the media through pre-existing fenestrations in the internal elastic lamina. Vasoconstriction may be involved in the pathogenesis of the arterial lesion. [Ref. VD 4206] |

* Doses are of fenoldopam unless otherwise specified.
** pgv = propylene glycol vehicle

Summary Table of Drug-Related Observations in Special Investigative Studies (Cont'd).

| Species | Duration of study | Doses | Observations |
|---|---|---|---|
| Rat | 24 hours | 2 mcg/kg/min hydralazine HCl,<br>20 mcg/kg/min Na nitroprussida,<br>5,20,50 and 100 mcg/kg/min dopamine,<br>100 mcg/kg/min<br>100 mcg/kg/min<br>100 mcg/kg/min<br>100 mcg/kg/min | To investigate the mechanism of the fenoldopam-induced arterial lesions.<br>Nine rats died at the highest dose of dopamine. I.V. infusion of dopamine produced lesions of the renal, splanchnic and coronary arteries of rats which were characterized by medial fibrinoid necrosis and occasional intramedial hemorrhages. Dopamine at the higher doses produced myocardial fiber damage. I.V. infusion of<br><br>produced medial necrosis and hemorrhage in renal and splanchnic arteries. No lesions occurred in coronary arteries or the myocardium. Rats appear to be highly susceptible to the vasculotoxic effects of dopaminergic compounds. [Ref. VD 4207] |
| Rat | 24 hours | 50 mcg/kg/min of fenoldopam for 1 and 4 hours, 20 mcg/kg/min of dopamine for 1, 4, and 24 hours | To extend morphologic observations by defining the ultrastructural characteristics of the arterial lesion produced by dopamine after 24 hours of infusion and to attempt to define early events in the pathogenesis of arterial lesions following 1 and 4 hour infusions of fenoldopam or dopamine.<br>Dopamine was more toxic to the arterial endothelium of rats than fenoldopam when administered by intravenous infusion at equivalent doses. Arterial lesions caused by dopamine were earlier in onset and progressed more rapidly than those induced by fenoldopam. Medial necrosis caused by dopamine was accompanied by deposition of fibrin which was probably related to the extent of damage to the arterial endothelium. This probably accounts for the qualitative morphologic differences observed between the arterial lesions caused by fenoldopam and dopamine. The formation of myofibrillar aggregates in medial smooth muscle cells of rats infused with dopamine and fenoldopam may be a common step in the pathogenesis of the arterial lesions caused by these compounds. [Ref. VD 4209] |
| Rat | 24 hours | 50 mcg/kg/min of fenoldopam or<br>20 mcg/kg/min of dopamine HCl | To survey by scanning electron microscopy (SEM) the luminal surface of gastric arteries of rats infused with fenoldopam or dopamine and to compare the onset, progression and extent of endothelial damage after 4 and 24 hour infusions.<br>Damage to endothelium was progressive; single, isolated endothelial cells being affected initially, followed by damage to many adjacent cells lining the vessel lumen. Damage to medial smooth muscle cells within the arterial wall was segmental in distribution. Dopamine caused more extensive damage to the endothelium cells than fenoldopam after infusion for 4 hours. Vasoconstriction may be involved in the pathogenesis of the arterial lesions caused by these two compounds. [Ref. TP002VD] |

Summary Table of Drug-Related Observations in Special Investigative Studies (Cont'd).

| Species | Duration of study | Doses | Observations |
|---|---|---|---|
| Rat | 24 hours | Each of the following alone and in combination with 50 mcg/kg/min of fenoldopam: 2 mcg/kg/min of hydralazine; 20 mcg/kg/min Na nitroprusside; 10 mg/kg phenoxybenzamine, s.c. | To determine whether vasoconstriction or medial smooth muscle cell hypercontraction is an important event in the pathogenesis of arterial medial necrosis and hemorrhage produced by i.v. infusion. The arterial lesion produced by fenoldopam administered in combination with nitroprusside, hydralazine or phenoxybenzamine was similar morphologically to that induced by fenoldopam alone. Vasoconstriction, caused either by direct action of fenoldopam, activation of alpha-adrenergic receptors, or by some other non-specific mediators, is not a primary cause of the arterial lesion induced by intravenous infusion of fenoldopam in the rat. [Ref. TP003VD] |
| Rat | 28 days | 24-hour infusion of either 50 mcg/kg/min of fenoldopam or 20 mcg/kg/min of dopamine with 3, 7, 14 and 28 day recovery time periods. | To determine the reversibility of fenoldopam- and dopamine-induced lesions following intravenous infusion and to define the changes which occur in the repair process. Arterial lesions caused by intravenous infusion of dopamine or fenoldopam in rats showed different patterns of repair and resolution. Large caliber splanchnic and renal arteries damaged by fenoldopam, though well repaired, showed evidence of medial hypertrophy and periarterial inflammation on day 28 post-infusion. Damage to small caliber splanchnic arteries caused by dopamine (medial fibrinoid necrosis) was completely resolved by day 14 post-infusion. Dopamine also produced an arterial lesion (medial necrosis and hemorrhage) which was similar morphologically to that casued by fenoldopam. [Ref. TP005VD] |
| Rat | 24 hours | 1, 50 mcg/kg/min fenoldopam; 50 mcg/kg/min dopamine; see Table B4 for doses of other compounds | To determine the role of dopaminergic and adrenergic receptors in the pathogenesis of the arterial lesion. Both dopamine and fenoldopam induced medial necrosis and hemorrhage of large caliber arteries as a result of activation of post-junctional, dopaminergic, $DA_1$ receptors. Blockade of alpha-adrenoceptors exacerbated the hemorrhagic lesions induced by both dopamine and fenoldopam. Blockade of alpha-adrenoceptors prevented damage to small caliber arteries and arterioles caused by dopamine. Co-administration of a dopaminergic $DA_1$ receptor antagonist (SK&F 83566-C), phenoxybenzamine ($alpha_1/alpha_2$ adrenoceptor and $DA_2$ dopaminergic receptor antagonist) and dopamine prevented development of hemorrhagic lesions in large caliber arteries and fibrinoid lesions in small caliber arteries caused by dopamine. [Ref. TP012VD] |

Comments: In the rat, I.V. administration of fenoldopam induced distinct medial smooth muscle necrosis and intramedial hemorrhagic lesions of large caliber arteries (greater than 100 um). These lesions were prevented or attenuated by a selective dopamine $DA_1$ receptor antagonist and are therefore believed to be caused by activation of post-junctional dopaminergic $DA_1$ receptors (See Fig. A on page 6 for a schematic representation of the arterial neuroeffector junction displaying locations of dopaminergic receptor subtypes). The lesions were confined to arteries of the renal and splanchnic vascular beds. When damaged large caliber splanchnic and renal arteries were allowed to recover, there was still evidence of medial hypertrophy and periarterial inflammation. Although medial smooth muscle cells are the principal target of fenoldopam-induced vasculotoxicity, alterations in endothelial cells may occur but these are believed to occur secondarily to damage to medial smooth muscle cells. The rat appears to be especially sensitive to this form of dopaminergic-mediated arterial lesion since the lesions have not been seen in dogs infused with fenoldopam or even dopamine. It must be noted that when 4 male monkeys were infused with 100 mcg fenoldopam/kg/min for 24 hrs, one animal showed intramedial necrosis and hemorrhage in a few arterioles of the gastric submucosa and a branch of the renal artery; however, no other arteries or arterioles of any other tissues were reported affected.

In rat, arterial lesions of the renal, splanchnic and coronary arteries induced by i.v. infusion of dopamine were characterized by medial fibrinoid necrosis and occasional intramedial hemorrhages. In addition, myocardial and coronary artery lesions were present in rats infused with dopamine 100 or 50 mcg/kg/min.

These studies confirmed that the arterial lesions in the rat were induced by fenoldopam and not by a secondary effect of the experimental procedure or the vehicle. Medial smooth muscle cells are the principal target of fenoldopam toxicity in the rat. While the pharmacologic activity and arterial toxicity of fenoldopam are linked in the rat, the biochemical events leading to arterial damage are not known.

Sponsor has provided in the NDA electron micrographs of the ultrastructural arterial lesions induced by the infusions of fenoldopam or dopamine in rats.

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REPRODUCTION STUDIES

Tabulation of Reproduction Studies Provided by Sponsor in this NDA.

| Species | Strain | No./Group | Mode of Administration | Doses | Study Duration | Laboratory |
|---|---|---|---|---|---|---|
| **SEGMENT I - Fertility and General Reproductive Performance Studies** | | | | | | |
| **Dose-Range Studies:** | | | | | | |
| Rat | CR CD | 6M | Oral Gavage | 25, 50, 75, 100, 125, 150, 200 mg/kg/day | See Note 1 | |
| Rat | CR CD | 10F | Oral Gavage | 25, 50, 75, 100, 125, 150, 200 mg/kg/day | See Note 3 | |
| **Definitive Studies:** | | | | | | |
| Rat | CR CD | 24M | Oral Gavage | 12.5, 37.5, 75.0 mg/kg/day | See Note 2 | |
| Rat | CR CD | 36F | Oral Gavage | 12.5, 37.5, 75.0 mg/kg/day | See Note 4 | |
| **SEGMENT II - Embryotoxicity/Developmental Toxicity** | | | | | | |
| Rat | CR CD | 8F | Oral Gavage | 12.5, 25, 50, 75, 100, 125, 150, 200, 250, 300 mg/kg/day | See Note 5 | |
| Rat | CR CD | 24F | Oral Gavage | 25, 100, 200 mg/kg/day | See Note 5 | |
| Rabbit | CR NZW | 6F | Oral Gavage | 12.5, 25, 50, 100, 200, 400, 600 mg/kg/day | See Note 6 | |
| Rabbit | CR NZW | 6F | Oral Gavage | 400 mg/kg/day | See Note 7 | |
| Rabbit | CR NZW | 24F | Oral Gavage | 6.25, 12.5, 25 mg/kg/day | See Note 6 | |
| **SEGMENT III - Peri-Postnatal Toxicity** | | | | | | |
| Rat | CR CD | 6F | Oral Gavage | 25, 50, 75, 100, 125, 150, 200 mg/kg/day | See Note 8 | |
| Rat | CR CD | 24F | Oral Gavage | 25, 50, 100 mg/kg/day | See Note 9 | |
| Rat | CR CD | 11-12 F1 litters | Not applicable | Not applicable | See Note 10 | |

Notes: 1) Males drug-treated for 21 days prior to mating, through mating to the end of the non-treated females' gestation (50 days).
2) Males drug-treated for 63 days prior to mating, through mating to the end of the non-treated females' gestation (94 days).
3) Females were drug-treated 11 days prior to mating, through mating to Day 20 of gestation for caesarean delivery or Day 6 of lactation for natural delivery.
4) Females were drug-treated 15 days prior to mating, throughout mating, to gestation Day 13 or Day 21 or at weaning on Day 28.
5) Females were drug-treated from Day 6 through Day 15 of gestation.
6) Females were drug-treated from Day 6 through Day 18 of gestation.
7) Females were drug-treated from Day 6 through Day 18 of gestation.
8) Females were drug-treated from Day 15 of gestation, through gestation to Day 6 of lactation.
9) Females were drug-treated from Day 15 of gestation to the end of gestation and to Day 20 of lactation.
10) F1 (delivered of F0, drug-treated parents, see Report VD 4603) were evaluated for physical and sexual development, fertility and reproductive performance.

Results of oral reproduction studies (FDA segments I, II and III) were previously submitted and reviewed under IND

According to these reviews a dose-range study in female rats revealed pallor and mottling of the kidneys in 10% of dams at 75 mg/kg/day, 40% of dams at 100 mg/kg and almost all of the females at 125 or more mg/kg with concomitant body weight loss at 100 mg/kg and above. A high dose of 75 mg/kg/day was selected for the definitive fertility studies. Fenoldopam produced no adverse effect on fertility and general reproductive performance (Segment I) of male or female rats.

To select the high-doses of fenoldopam for Segment II studies, sponsor performed dose-range studies in rat and rabbit. In addition, an oral toxicity study with fenoldopam (400 mg/kg/day) was performed in pregnant rabbits (not Segment II). Fenoldopam was suspended in a mixture of methylcellulose, PEG 400 and Tween 80. All drug treated rabbits died; gross observations revealed varying degrees of gastric mucosa erosion. It was concluded that the lethal effects were similar to those observed when the drug was suspended in 0.5% tragacanth.

In the rat teratology study, oral doses of 25 or 100 mg fenoldopam/kg/day (on days 6-15 of pregnancy) produced no evidence of maternal toxicity. The high-dose (200 mg/kg/day based on a dose-range study) caused a reduction (33%) in average food consumption and decrease (11%) in maternal body weight gain when compared to corresponding controls throughout same dosing period; there was some recovery during the post-treatment. The high-dose fetuses showed a decrease (8% less than the control) in the average birth weights and is considered related to the maternal toxicity. There was some difference between control and high-dose fetuses in the occurrence of some skeletal deviations (i.e, hypoplastic sternal centers- 8%, wavy ribs- 3%, incomplete ossification of metatarsals- 21%). Although these skeletal variations were higher than in the controls, their incidences are still considered to be within the normal range.

In the rabbit teratology study, oral doses of 6.25, 12.5 or 25 mg fenoldopam/kg/day (days 6-18 of pregnancy) produced no evidence of drug toxicity in the dams. Two malformed fetuses (delivered by Caesarean section on day 29 of gestation) were reported in each of the control, low-dose and high-dose groups and 1 was reported in the mid-dose group. Except for one observation in the control group (1 fetus with spina bifida* and clubbed limbs), malformations (i.e., acephaly complicated with anomalies of the extremities, abdomen, and/or thorax, gastroschisis, ectrodactyly, umbilical hernia and bilateral forelimb flexure) in test groups have been observed in previous control groups and their rates were within the historical control limits.

Regarding peri- and postnatal studies (Segment III) in pregnant rat, although there were slight decreases in food consumption/body weight gain in the high-dose dams, oral administration of fenoldopam (25, 50 or 100 mg/kg/day) had no adverse effect on fetal development, labor, delivery, lactation or viability and growth of the offspring. Skeletal examination of stillborn and pups that died during lactation revealed slight delay in ossification in 1 of 8 controls, 3 of 12 low-, 6 of 18 mid-, and 1 of 5 high-dose group pups.

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**Spina bifida cystica had not been previously seen in sponsor's laboratory in Charles River rabbits.

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MUTAGENICITY

Summary/evaluation of Ames test (previously submitted) with fenoldopam was performed by preceding pharmacologist R. M. Mhatre, Ph.D.

Tabulation of Studies and Summary of Results from Mutagenicity Studies (Provided by sponsor).

| Study | Concentrations (Doses) Tested | Results |
|---|---|---|
| IN VITRO: | | |
| Ames Assay [1] [2] | 0.5, 1.0, 10, 100, 500, 1000 mcg(salt)/ml w/wo[3] S-9 | Negative for mutagenic activity. |
| CHO/HGPRT Mammalian Cell Forward Gene Mutation Assay [1] [2] | 10, 20, 35, 50, 75 mcg(salt)/ml wo/S-9<br>50, 75, 100, 250, 500 mcg(salt)/ml w/S-9 | Negative for mutagenic activity. |
| Chromosome Aberration Analysis in Chinese Hamster Ovary (CHO) Cells [1] [2] | 25, 100, 200, 250 mcg(salt)/ml wo/S-9<br>55, 175, 500, 550 mcg(salt)/ml w/S-9 | Statistically significant, dose-dependent increase in chromosome aberrations and proportion of aberrant metaphases at all dose levels with S-9. Statistically significant increase in chromosome aberrations and proportion of aberrant metaphases at 100 and 250 mcg/ml only, without S-9. |
| IN VIVO: | | |
| [illegible]ucleus Test [1] [2] | 125 mg/kg, i.p. | Negative for mutagenic activity. |
| Dose-Range Study for Bone Marrow Cytogenetics in Mice [1] [2] | 10, 80, 100, 125, 150 mg/kg, i.p. | Not a test for mutagenic potential. Indication of cellular toxicity (increase in mean proliferation time) seen in females (100, 125 and 150 mg/kg) and males (100 mg/kg). High-dose selected for definitive assay, females 140 mg/kg and males 160 mg/kg. |
| Bone Marrow Cytogenetics in Mice [1] [2] | 35, 70, 140(F), 160(M) mg(salt)/kg, i.p. | Negative for mutagenic activity. |

[1] [2] w/wo = with/without

Comments:

Fenoldopam did not induce either reverse or forward gene mutations when tested in bacterial and mammalian cell assays and was considered not to be mutagenic. However, when tested in vitro for its ability to induce chromosomal aberrations in Chinese hamster ovary (CHO) cells, fenoldopam did produce a statistically significant and concentration dependent increase (p less than 0.05) in aberrations both in the presence and absence of a metabolic activation system; no significant effect was noted at the low concentration of 25 ug/ml. Based on the results of this assay, the drug was judged positive in the in vitro chromosome aberration test. The reason for the positive finding in this assay is not known. Sponsor speculates that "it is possible that some genotoxic substance was produced in vitro which was unique to the culture conditions or that a short-lived genotoxic substance, such as a highly reactive oxygen species, was produced in vitro which would not have been able to form in enough quantity and/or for long enough in vivo to produce an effect, due to the protective repair enzymes found in vivo. Fenoldopam did not induce chromosomal aberrations in vivo.

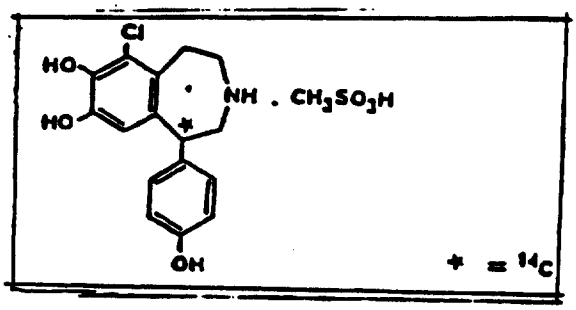
PHARMACOKINETICS

Summary/evaluations of pharmacokinetic studies previously submitted were performed by 2 preceding pharmacologists (Drs. Gar Bo Ho and W. C. Van Arsdel)

Tabulation and Summary of Pharmacokinetic and Metabolism Studies with Fenoldopam (Provided by sponsor).

Where $^{14}C$-fenoldopam was used, the drug was labelled in the position shown in Fig. 2. below. The specific activity ranged from 15.5 to 31.7 uCi/mg.

Fig. 2 $^{14}C$-fenoldopam




| Study Type [References] | Species | n | Dose Route | Results |
|---|---|---|---|---|
| ANALYTICAL METHODS | | | | |
| GLC [216] | - | - | - | Fenoldopam in plasma, alkaline extracted with ethyl acetate, acidified and derivatized with pentafluoropropionic anhydride. Sensitivity 50 ng/ml. |
| HPLC [218, 219] | - | - | - | HPLC with electrochemical detection, fenoldopam and methoxy metabolites alkaline extracted with ethyl acetate then with mobile phase buffer. Linear between 0-100 ng/ml plasma. Limits of detection for fenoldopam- 10-25 pg/ml, for methoxy metabolites- 1 ng/ml. |
| Stability of fenoldopam in *ex vivo* plasma [217] | - | - | - | Room temperature samples with added ascorbic acid and EDTA - rapid degradation. Samples frozen (-20°C) plus added ascorbic acid and EDTA - stable for 1 month but samples deteriorated beyond this time. |
| PHARMACOKINETICS AFTER A SINGLE DOSE | | | | |
| Bioavailability and plasma concentrations [225] | Mouse | 10M-10F | 50 mg/kg p.o. | Plasma $^{14}C$, $C_{MAX}$ - 32.1,38.0 mcg/ml, males and females, respectively. Parent drug plasma $C_{MAX}$ - 0.48, 0.50 mcg/ml males and females, respectively. Bioavailability of $^{14}C$ - 28%, unchanged drug - 19%. |
| Bioavailability and plasma concentrations [220, 222] | Rat | 6M | 25 mg/kg p.o. | Plasma parent drug $C_{MAX}$ - 0.88 mcg/ml |
| | | 3M | 38 mg/kg p.o. | Plasma $^{14}C$, $C_{MAX}$ - 9.40 mcg/ml. Plasma parent drug - 0.10 mcg/ml |
| | | 3M | 50 mg/kg p.o. | Plasma parent drug $C_{MAX}$ - 0.18 mcg/ml<br>Bioavailability of $^{14}C$-69%; unchanged drug - 2% |
| Bioavailability and plasma concentrations [220, 221] | Dog | 3M | 10 mg/kg p.o. | Plasma parent drug $C_{MAX}$ - 0.35 mcg/ml |
| | | 3M | 20 mg/kg p.o. | Plasma parent drug $C_{MAX}$ - 1.55 mcg/ml |
| | | 3M | 20 mg/kg p.o. | Plasma $^{14}C$, $C_{MAX}$ - 17.9 mcg/ml. Plasma parent drug - 1.77 mcg/ml |
| | | 4F | 10 mg/kg p.o. | Plasma parent drug $C_{MAX}$ - 0.29 mcg/ml |
| | | 2F | 20 mg/kg p.o. | Plasma parent drug $C_{MAX}$ - 0.75 mcg/ml |
| | | 3F | 20 mg/kg p.o. | Plasma $^{14}C$, $C_{MAX}$- 17.8 mcg/ml. Plasma parent drug - 1.80 mcg/ml. Bioavailability of $^{14}C$ - 79%, unchanged drug - 32% |
| Absorption of fenoldopam in presence of food [226] | Mouse | 36M | 74 mg/kg by gavage, | Plasma fenoldopam concentrations variable when administered in purina chow but at times were within range of dose given by gavage, indicating that absorption took place. |
| | | 36F | 1 mg/g of food | |

## Tabulation and Summary of Pharmacokinetic and Metabolism Studies with Fenoldopam (Cont'd).

| Study Type [Report No.] | Species | n | Dose Route | Results |
|---|---|---|---|---|
| **PHARMACOKINETICS AFTER A SINGLE DOSE (cont'd)** | | | | |
| Absorption of fenoldopam in presence of food [VD 3001] | Rat | 8OM | 50 mg/kg by gavage<br>54 mg/kg with food | Plasma fenoldopam concentration extremely variable when administered in purina chow, in many cases not detectable. Concentrations were extremely low as compared to dose by gavage. |
| Site of intestinal absorption [VD 3002] | Dog | 4M | 20 mg/kg | Plasma concentrations of $^{14}C$, following instillation of fenoldopam into closed intestinal sacs of anesthetized dogs, indicated that absorption was greatest from jejunum. Relative to the jejunum, absorption from other intestinal sections were: jejunum- 1.00, duodenum- 0.55, ileum- 0.26, colon- 0.16. |
| Elimination of drug related material & fenoldopam from the circulation [VD 3005, VD 3006, VD 3007, VD 3020, BP014VD, BP015VD] | Mouse | 100M<br>100F<br>100M<br>100F | 10 mg/kg i.v.<br>10 mg/kg i.v.<br>50 mg/kg p.o.<br>50 mg/kg p.o. | Unchanged fenoldopam was rapidly eliminated from plasma but total drug-related material declined more slowly. Blood and plasma concentration-time profiles were usually multi-exponential. Means of $t_{1/2}$ of terminal phase are shown below: |
| | Rat | 64M<br>30M | 10 mg/kg i.v.<br>38 mg/kg p.o. | |
| | Dog | 3M<br>3F<br>4M<br>4M<br>3M<br>3F | 1 mg/kg i.v.<br>1 mg/kg i.v.<br>1 mg/kg i.v.<br>10 mg/kg p.o.<br>20 mg/kg p.o.<br>20 mg/kg p.o. | |
| **Plasma concentration in single dose path/tox studies:** | | | | |
| 24-hr intravenous infusion [VD 3508] | Rat | 8M, 8F | 1, 5, 25, 100 mcg/kg/min i.v. | Plasma fenoldopam concentrations were quite variable both within and between species. At some of the low infusion rates concentrations were below GLC method sensitivity. Rat and monkey concentration, at same infusion rates, were within similar ranges but dog data approximately 5 times higher. Example: 24-hr infusion at 100 mcg/kg/min, rat 12-145, dog 1770, monkey 271 ng/ml. |
| 6-hr, 24-hr intravenous infusion [VD 3502, VD 3503] | Dog | 1M,1F (6-hr)<br>2M,2F (24-hr) | 1, 5, 25, 100 mcg/kg/min i.v.<br>5, 50, 100 mcg/kg/min i.v. | |
| 24-hr intravenous infusion [VD 3512] | Monkey | 4M (24-hr) | 5, 50, 100 mcg/kg/min i.v. | |

| | Radioactivity blood | Radioactivity plasma | Fenoldopam plasma |
|---|---|---|---|
| mouse i.v. | 11.2-11.5 hr | 6.7-6.8 hr | -[A] |
| mouse p.o. | 2.5-5.3 hr | 1.9-3.3 hr | - |
| rat i.v. | 9 hr | 5 hr | - |
| rat p.o. | 6 hr | 5 hr | - |
| dog i.v. | 1.9 hr | 1.9 hr | 0.6-1.6 hr |
| dog p.o. | 1.5-1.8 hr | 1.4-1.8 hr | 1.1-1.8 hr |

[A] terminal $t_{1/2}$ not measurable

## Tabulation and Summary of Pharmacokinetic and Metabolism Studies with Fenoldopam (Cont'd).

| Study Type | Report No.] | Species | n | Dose Route | Results |
|---|---|---|---|---|---|
| **PHARMACOKINETICS AFTER A SINGLE DOSE (cont'd)** | | | | | |
| Plasma concentrations during 3-hr infusion studies | [BP010VD] | Rat* | 4M/dose | 10, 25, 50, 100 mcg/kg/min i.v. | Steady-state plasma fenoldopam concentrations were achieved in 30 minutes. At infusion rates used, mean steady-state concentrations were linear ranging from that achieved at low dose, 25.6, to that of high dose, 340 ng/ml. Systemic clearance at steady-state, over the concentration range infused, was 328 ml/min/kg. |
| Plasma concentrations during 6-hr infusion studies | [BP012VD] | Dog* | 2M,2F | 5, 50 mcg/kg/min i.v. | Steady-state plasma fenoldopam concentrations were proportional to dose at 72 and 761 ng/ml. Systemic clearance at both doses was 73 ml/min/kg. Terminal elimination $t_{1/2}$ was 12 min following cessation of 6-hr infusions. |
| Plasma concentrations in pregnant rabbits | [VD 3589] | Rabbit | 10F/dose | 50, 400 mg/kg i.v. | Rabbits were of same strain as used in teratology studies. Plasma $T_{MAX}$- 15min, $C_{MAX}$- 284 ng/ml and $T_{MAX}$- 6-hr, $C_{MAX}$- 2390 ng/ml for 50 and 400 mg/kg doses, respectively. |
| Excretion of radioactivity over 4-day period | [VD 3028] | House | 10M<br>10F<br>10M<br>10F | 10 mg/kg i.v.<br>10 mg/kg i.v.<br>50 mg/kg p.o.<br>50 mg/kg p.o. | Urine, 77% - Feces, 28% of dose<br>Urine, 56% - Feces, 43% of dose<br>Urine, 22% - Feces, 84% of dose<br>Urine, 15% - Feces, 81% of dose |
| Excretion of radioactivity over 4-day period | [VD 3089] | Rat | 6M<br>6F | 1 mg/kg i.v.<br>25 mg/kg p.o. | Urine, 51% - Feces, 48% of dose<br>Urine, 35% - Feces, 58% of dose |
| Excretion of radioactivity over 4-day period | [BW001VD] | Rat | 3M | 10 mg/kg i.v. | Urine, 43% - Feces, 55% of dose |
| Excretion of radioactivity over 4-day period | [VD 3086] | Dog | 3M<br>3F<br>3M<br>3F | 1 mg/kg i.v.<br>1 mg/kg i.v.<br>20 mg/kg p.o.<br>20 mg/kg p.o. | Urine, 56% - Feces, 34% of dose<br>Urine, 75% - Feces, 27% of dose<br>Urine, 42% - Feces, 49% of dose<br>Urine, 63% - Feces, 23% of dose |
| Biliary excretion | [BP008VD] | Rat | 4M | 10 mg/kg i.v. | Within 24 hours, 62.1, 32.7, 1.8% of the administered $^{14}C$ dose was excreted in bile, urine and feces, respectively. |
| | | Rat | 3M | 38 mg/kg p.o. | Within 24 hours, 30.5, 20.4, 18.9% of the administered $^{14}C$ dose was excreted in bile, urine and feces, respectively. |

* See Table 7 provided by sponsor for sub-chronic/chronic blood level studies in rat and dog.

## Tabulation and Summary of Pharmacokinetic and Metabolism Studies with Fenoldopam (Cont'd).

| Study Type | Report No.] | Species | n | Dose Route | Results |
|---|---|---|---|---|---|
| **PHARMACOKINETICS AFTER REPEATED ADMINISTRATION** | | | | | |
| Dose proportionality excretion of 7-beta glucuronide metabolite( $F_7G$) after 7 days of fenoldopam [VD 3029] | | Rat | 5M/dose | 2, 20, 40, 80, 160 mg/kg/day for 7 days, p.o. | $F_7G$, as % of urinary radioactivity, declined from 63% (Day 1) to 38% (Day 7). $F_7G$ proportional to dose on Day 1-4 (2 mg to 160 mg/day) but on Day 7 there was a reduction in ratio of $F_7G$ to dose, in top-dose group. $F_7G$ precipitated spontaneously from urine from 40 mg/kg dose and above, but incidence decreased with time. Drug-induced renal lesions were seen in top-dose rats only. No correlation between renal lesions and incidence of precipitation or concentration of $F_7G$ was found. |
| Plasma concentrations in repeated dose path/tox studies [VD 3585] | | Rat | 15M,15F per dose | 12.5, 25, 87.5 mg/kg,p.o. during 3 mo.study | In general, plasma fenoldopam concentrations (when measurable) increased as the administered dose was increased. Concentrations in the rat, after p.o. dose, were lower than in dogs, at similar dose rates. Many plasma concentrations in rats were below the GLC analytical sensitivity limits. Mean concentrations in the dog, after repeated i.v. or p.o. doses, were in approximate proportion to dose. Plasma fenoldopam concentrations were an indication of fenoldopam absorption in the p.o. studies. |
| Plasma concentrations in repeated dose path/tox studies [VD 3586] | | Rat | 20M,20F per dose | 15,25,40mg/kg,p.o. during 1 yr study | |
| Plasma concentrations in repeated dose path/tox studies [VD 3584] | | Dog | 3M, 3F per dose | 5,50,100mcg/kg/min 6 hr for 14 days, i.v. infusion | |
| Plasma concentrations in repeated dose path/tox studies [VD 3585] | | Dog | 3M, 3F per dose | 6.25,18,48 mg/kg/ day, p.o. during 3 mo. study | |
| Plasma concentrations in repeated dose path/tox studies [VD 3613] | | Dog | 4M, 4F per dose | 10,20,120 mg/kg/day, p.o. during 1 yr study | |
| **DISTRIBUTION IN NORMAL AND PREGNANT ANIMALS** | | | | | |
| Binding of $^{14}C$ to blood cells after $^{14}C$-fenoldopam (in vivo) [VD 3005, VD 3006, VD 3007, VD 3028] | | House | 100M, 100F | 10 mg/kg, i.v. | Binding of total $^{14}C$ to blood cells immediately after i.v. dosing - 40%, after p.o. dosing - 6% or less. |
| | | | 100M, 100F | 50 mg/kg, p.o. | |
| | | Rat | 64M | 10 mg/kg, i.v. | Binding of total $^{14}C$ to blood cells immediately after i.v. dosing - 80%, after p.o. dosing - 6% or less. |
| | | | 30M | 38 mg/kg, p.o. | |
| | | Dog | 3M/3F | 1 mg/kg, i.v. | Initial binding of total $^{14}C$ to blood cells was 31-38% after i.v. and p.o. doses respectively, then fell to 3-17% after 1-4 hours. Binding then increased to reach, at 24 hours, values similar to initial binding. |
| | | | 3M/3F | 20 mg/kg, p.o. | |
| Secretion of $^{14}C$ into milk of lactating rats after $^{14}C$-fenoldopam [VD 3027] | | Rat | 5F | 25 mg/kg p.o. | Milk collected 0.5 to 2.5 hours after dose. Milk $^{14}C$ was 3.1% of the 0.5 hour plasma $^{14}C$ and 9.8% of the 2.5 hour plasma $^{14}C$ concentration. $^{14}C$ was secreted into milk but no evidence of a concentration above that of plasma was found. |

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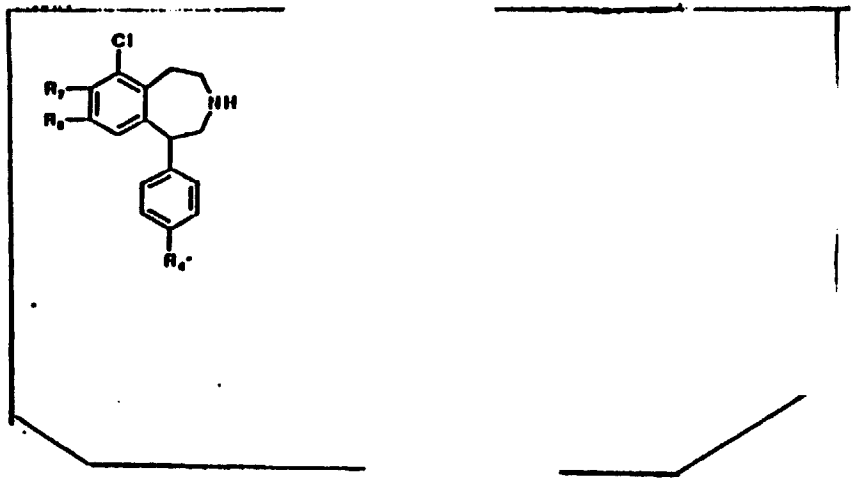
## Tabulation and Summary of Pharmacokinetic and Metabolism Studies with Fenoldopam (Cont'd).

| Study Type | Report No.] | Species | n | Dose Route | Results |
|---|---|---|---|---|---|
| DISTRIBUTION IN NORMAL AND PREGNANT ANIMALS (cont'd) | | | | | |
| Distribution of $^{14}C$ in blood after $^{14}C$-fenoldopam | [VD 3025] | Rat | | in vitro 0.1-12 mcg/ml | At the lowest concentration, 64% of the $^{14}C$ was associated with blood cells in all 3 species of blood. At the highest concentration the % increased to 70% in human and 80% in rat and dog blood. Unbound $^{14}C$ was 5.9%, 8.5% and 6.3% in human, rat and dog, respectively. Remaining $^{14}C$ was bound to plasma proteins. |
| | | Dog | | in vitro 0.1-12 mcg/ml | |
| | | Human | | in vitro 0.1-12 mcg/ml | |
| Binding of $^{14}C$ to plasma proteins after $^{14}C$-fenoldopam | [VD 3025] | Rat | | in vitro 0.01-2 mcg/ml | Plasma protein binding of $^{14}C$ in rat - 72.7%, dog - 80.1%, human - 88.3%. Major binding protein was albumin, with indication of only one binding site. |
| | | Dog | | in vitro 0.01-2 mcg/ml | |
| | | Human | | in vitro 0.01-2 mcg/ml | |
| Tissue distribution of $^{14}C$ after $^{14}C$-fenoldopam | [VD 3008] | Rat | 2M | 5 mg/kg i.v. | Autoradiographs 5 minutes after dose showed $^{14}C$ in all tissues except CNS. Highest concentrations in kidney, bladder, heart, lungs, liver and adrenal glands. |
| Tissue distribution of $^{14}C$ after $^{14}C$-fenoldopam | [BW001VD] | Rat | 16M | 10 mg/kg i.v. | Peak of $^{14}C$ concentration at 1 hour in all tissues examined. Highest concentrations in small intestine, kidney, liver and gastrointestional contents. By 72 hours, excretion of dose was complete at 100.6% of dose. |
| Distribution of $^{14}C$ in pigmented and albino eyes after $^{14}C$-fenoldopam | [BW001VD] | Rat (Pigmented) | 15M | 10 mg/kg i.v. | Following i.v. administration, at 1 hour, $^{14}C$ in pigmented eyes was 3-fold higher than in albino eyes. $^{14}C$ in both eyes declined at a rate such that $^{14}C$ in pigmented eyes was 22-fold higher than in albino eyes, 72 hours after dose. Following p.o. administration, $^{14}C$ was detectable at 1 hour but, by 14 days, no $^{14}C$ was detectable in pigmented or in albino eyes. |
| | | Rat (pigmented) | 15M | 40 mg/kg p.o. | |
| | | Rat (albino) | 16M | 10 mg/kg i.v. | |
| | | Rat (albino) | 6M | 40 mg/kg p.o. | |
| Tissue distribution of $^{14}C$ after $^{14}C$-fenoldopam | [VD 3007] | Rat | 30M | 30 mg/kg p.o. | $^{14}C$ content at all tissues examined, except gastrointestinal tract, kidneys and liver, was less than blood and plasma concentrations. Elimination of $^{14}C$ from exceptional tissues was at a rate similar to that of blood and plasma. |
| Tissue distribution of $^{14}C$ in pregnant rat after $^{14}C$-fenoldopam | [BP003VD] | Rat | 3F | 25 mg/kg p.o. | Autoradiographic study was carried out on the 20th gestation day, 1 hour after dose. Tissue $^{14}C$ distribution was similar to non-pregnant rat. No $^{14}C$ concentration in specific fetal organs. CNS of fetuses contained less $^{14}C$ than did surrounding tissues. |

## Tabulation and Summary of Pharmacokinetic and Metabolism Studies with Fenoldopam (Cont'd).

Structures of Fenoldopam and its Metabolites




| Study Type | Report No.] | Species | n | Dose Route | Results |
|---|---|---|---|---|---|
| **BIOTRANSFORMATION** | | | | | |
| Identification of metabolites in urine [VD 3018, VD 3016, VD 3026] | | Mouse | 10M | 10 mg/kg i.v. | Urinary metabolite profile* indicated that the same pathways were utilized by the mouse, rat and dog. Major metabolite was 7-beta glucuronide in mouse and rat but was insignificant in dog. Sulfate conjugation was minor in mouse and rat but major in the dog. In all 3 species, O-methylation to form 7- and 8-methoxy fenoldopam was a minor pathway. Methoxy metabolites were mainly conjugated as sulfates in dog but were only partially conjugated in the mouse and rat. |
| | | | 10F | 10 mg/kg i.v. | |
| | | | 10M | 60 mg/kg p.o. | |
| | | | 10F | 60 mg/kg p.o. | |
| | | Rat | 6M | 10 mg/kg i.v. | |
| | | | 6M | 25 mg/kg p.o. | |
| | | Dog | 3M | 1 mg/kg i.v. | |
| | | | 3F | 1 mg/kg i.v. | |
| | | | 3M | 20 mg/kg p.o. | |
| | | | 3F | 20 mg/kg p.o. | |
| Identification of urinary crystals produced following fenoldopam [VD 3026, VD 3500, VD 3501] | | Mouse | - | 200 mg/kg/day, p.o. | Spontaneous urinary crystals were isolated from urine of mice, on 200 mg/kg/day in 3 month chronic tox study, from rats on 40 mg/kg/day in 12 month chronic tox study and from the 60-130 mg/kg/day group of the 3 month subacute tox study. Crystals were identified as the 7-beta glucuronide conjugate of fenoldopam. |
| | | Rat | - | 40 mg/kg/day, p.o.<br>60-130 mg/kg/day p.o. | |
| Metabolites in Gunn Rat urine [VD 3028] | | Rat | 3 | 131 mg/kg p.o. | Gunn rats are known to exhibit low glucuronyltransferase activity. However, about 50% of the total dose of fenoldopam was excreted as the 7-beta-glucuronide of fenoldopam in these rats. |
| Reversible metabolism of fenoldopam (F) and the fenoldopam sulfated conjugates ($F_7S$, $F_8S$) [DP014VD] | | Dog | 4M | 1 mg/kg (F) i.v. | Pharmacokinetic parameters: |
| | | | 4M | 4.4 mg/kg ($F_7S$) | |
| | | | 4M | 4.4 mg/kg ($F_8S$) | |

| | $V_B$ (l/kg) | $t_{1/2}$ (min) | $Cl_R$ (ml/min/kg) |
|---|---|---|---|
| F | 1.6 | 96.2 | 8.47 |
| $F_7S$ | 0.3 | 90.4 | 1.92 |
| $F_8S$ | 0.3 | 85.4 | 1.60 |

In these studies 2.9% of administered $F_7S$ and 1.1% of $F_8S$ were converted back to fenoldopam after i.v. infusion of $F_7S$ and $F_8S$.

Tabulation and Summary of Pharmacokinetic and Metabolism Studies with Fenoldopam (Cont'd).

| Study Type [Report No.] | Species | n | Dose Route | Results |
|---|---|---|---|---|
| **BIOTRANSFORMATION** (cont'd) Metabolites in monkey urine and plasma [VD 3812] | Monkey | 4M<br>4M<br>4M | 5 mcg/kg/min i.v.<br>50 mcg/kg/min i.v.<br>100 mcg/kg/min i.v. | Fenoldopam was infused for 24 hours in an intravenous toxicity study. Plasma concentrations of fenoldopam were linear over the dose range. The ratios of fenoldopam, 7-beta glucuronide and sulfate conjugates to their combined total in 24 hour urine were 0.26, 0.30, 0.44, respectively, at low dosage and 0.54, 0.21, 0.26 at the highest dosage. |
| Metabolites in bile [VD 3811] | Rat | 3M<br>4M | 10 mg/kg i.v.<br>30 mg/kg p.o. | Major metabolites in bile after i.v. dose were sulfate conjugates. After p.o. dose metabolites were 7-beta glucuronides. O-methylated metabolites were major after i.v. but minor after p.o. doses. O-methylated metabolites were conjugated mostly as sulfates. |
| **DRUG INTERACTIONS** | | | | |
| Effect of fenoldopam on hepatic drug-metabolizing enzymes [VD 3824] | Rat | 3M<br>3M<br>3M<br>3M<br>3M<br>3M | 3 mg/kg p.o., 3 days<br>32 mg/kg p.o., 3 days<br>100 mg/kg p.o., 3 days<br>3 mg/kg p.o., 14 days<br>32 mg/kg p.o., 14 days<br>100 mg/kg p.o., 14 days | Hepatic enzymes measured were P450, benzphetamine-N-demethylase, ethoxycoumarin-O-deethylase, epoxide hydrolase, DT-diaphorase. No changes in growth rate, serum ALT activity or hepatic enzymes were found that were considered to be of biological significance. |
| Effect of acetaminophen-induced sulfate depletion on fenoldopam pharmacokinetics and metabolism [BP81SVD] | Dog | 12M | 125 mg p.o. | Acetaminophen at 325, 500 or 1000 mg, t.i.d. for 3 days, drastically reduced plasma inorganic sulfate levels. When 125 mg fenoldopam was given on the 3rd day of 1000 mg acetaminophen, the AUC of plasma fenoldopam increased 250% over baseline values, accompanied by a 67% decrease in fenoldopam-8-sulfate AUC. The 7- and 8-methoxy metabolites increased in proportion to the increase AUC of fenoldopam. Fenoldopam $t_{1/2}$ remained the same before and after acetaminophen, 1.8 ± 0.6 hr. |

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Table 7

Mean (± SD) Steady-State Plasma Concentrations of Fenoldopam Following Intravenous Infusion at Different Rates

| Infusion Rate (mcg/kg/min) | Rat[a] (n=4) | Dog[b] (n=4) | Man[c] (N=30) |
|---|---|---|---|
| 0.025 | – | – | 1.0 ± 0.2 |
| 0.05 | – | – | 1.6 ± 0.3 |
| 0.1 | – | – | 2.9 ± 0.8 |
| 0.25 | – | – | 6.1 ± 1.3 |
| 0.5 | – | – | 12.4 ± 1.7 |
| 1.0 | – | – | 24.3 ± 3.9 |
| 5 | – | 72 ± 8 | – |
| 10 | 25.6 ± 2.0 | – | – |
| 25 | 79.8 ± 28.6 | – | – |
| 50 | 180.6 ± 26.2 | 761 ± 96 | – |
| 100 | 339.6 ± 48.9 | – | – |

[a] BP010VD
[b] BP012VD
[c] Pooled Data From Protocols L-34, L-64, A-21.

Table 8

Urinary Excretion[a] of Fenoldopam and Metabolites After Oral or Intravenous Administration of Fenoldopam to Animals and Man (Expressed as % Dose of Fenoldopam)

| Species/dose/sex | Fenoldopam | Fenoldopam[b] Glucuronide Conjugate | Fenoldopam Sulfate Conjugates | Methoxy[c] Fenoldopam |
|---|---|---|---|---|
| **Mouse** | | | | |
| 50 mg/kg, p.o., M | N.D. | 15.4 | [d] | 4.8 |
| 50 mg/kg, p.o., F | N.D. | 18.5 | [d] | 1.9 |
| 10 mg/kg, i.v., M | N.D. | 27.8 | 12.1 | 28.5 |
| 10 mg/kg, i.v., F | N.D. | 21.6 | 9.9 | 17.9 |
| **Rat** | | | | |
| 25 mg/kg, p.o., M | 2.4-8.6 | 8.9-27.8 | 8.7-2.8 | 1.4-16.4 |
| 10 mg/kg, i.v., M | 1.5-2.5 | 14.8-17.4 | 1.5-2.8 | 6.5-25.8 |
| **Dog** | | | | |
| 20 mg/kg, p.o., M | 6.8-7.4 | N.D.[e] | 16.8-17.8 | 3.3-4.8 |
| 20 mg/kg, p.o., F | 15.8-16.4 | N.D. | 35.1-35.6 | 3.3-6.6 |
| 1 mg/kg, i.v., M | 1.5 | N.D. | 15.9-17.4 | 8.6-12.5 |
| 1 mg/kg, i.v., F | 2.2-2.9 | N.D. | 24.8-27.7 | 14.6-17.5 |
| 1 mg/kg, i.v., M | 6.45 | 1.3 | 16.6 | 18.7 |
| **Monkey** | | | | |
| 5 mcg/kg/min/24 hr, i.v. | 3.8 | 3.2 | 5.6 | not measured |
| 50 mcg/kg/min/24 hr, i.v. | 6.8 | 6.4 | 4.6 | not measured |
| 100 mcg/kg/min/24 hr, i.v. | 7.2 | 2.9 | 3.5 | not measured |
| **Man (mean)[f]** | | | | |
| 50 mg (n=6), p.o. | 6.9 | 12.7 | 26.8 | 5.1 |
| 100 mg (n=56), p.o. | 1.1 | 13.2 | 21.2 | 7.6 |
| 200 mg (n=6), p.o. | 6.8 | 19.8 | 17.5 | 5.9 |
| 2 to 10 mg (n=12), i.v. | 5.1 | 18.1 | N.D.-6.8 | 28.4 |

[a] 6-24 hour collection interval
[b] fenoldopam released by beta-glucuronidase
[c] 7- and 8-6-methyl-fenoldopam released by glucuronidase and sulfatase
[d] small unquantified amounts
[e] ND - not detectable
[f] mean of means (of the same administered doses) from different studies

LOCAL TOLERANCE STUDIES

Summary/evaluation of previously submitted irritation studies was performed by by Gar Bo Ho, Ph.D.

Tabulation of Local Tolerance Studies Provided by Sponsor in this NDA.

| Species | Duration of Study | Doses | Observations |
|---|---|---|---|
| Rabbit | 5 days | 100 mg in powdered form (eye)<br>500 mg in powdered form (skin) | Slight to moderate redness and swelling of the eyelids and slight redness of the sclera with or without irrigation were observed after instillation of the drug. These effects decreased in severity daily. The eyes appeared normal by Day 5 following drug application. No visible signs of irritation were observed when fenoldopam was applied topically to the denuded skin (back) of rabbits. [Refs. VD 4102, VD 4103] |
| Dog | 2 days | 0.1, 1.0, 10 mg/kg in 40% pgv*; 2ml/injection | A single injection of fenoldopam at 0.1 and 1.0 mg/ml did not produce irritation of the veins, perivenous, perineural or muscular tissue. Both the undiluted drug formulation (10 mg/ml) and placebo, produced necrosis and thrombosis in small subcutaneous vessels when administered perivenously, and when given intramuscularly, caused severe muscle and vascular degeneration and inflammatory change. There was no adverse effect when the undiluted formulation was given either intravenously or perineurally. [Ref. VD 4100] |
| Dog | 8 days | 8 mg/ml in 8% pgv*; 8 mg/ml in 0.9% saline; 2 ml/injection | Fenoldopam, at a dose of 8 mg/ml in 8% pgv, did not injure veins and was not unduly irritating to subcutaneous tissue when injected perivenously. Minor changes observed in the muscle were qualitatively similar to those observed in the controls. [Ref. VD 4101] |

* pgv = propylene glycol vehicle

Comments: The injectable formulations tested were different from the solution proposed for marketing.

LABELING:

The following recommendations are made with respect to the proposed package insert:

Under the heading "Carcinogenesis/Mutagenesis/Impairment of Fertility,"

a) the description of the 24 month mouse study should be revised to read as follows: "In a 24-month study, mice treated orally with fenoldopam at 12.5 or 25 mg/kg/day, or with 50 mg/kg/day reduced to 35 mg/kg/day on day 209, showed no increase above control in incidence or type of neoplasms. Female mice of the highest dosage group had an increase in incidence and degree of severity of a fibro-osseous lesion of the sternum. Female mice in the middle and high dose groups had a higher incidence and degree of severity of chronic nephritis than did control mice."

b) The following statement on fertility should be added to this section: "Oral reproductive performance studies in male and female rats at doses up to 75 mg/kg/day have revealed no impairment of fertility."

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SUMMARY AND EVALUATION:

Fenoldopam is a benzazepine derivative structurally related to the catecholamine dopamine. The drug has

inactive. Fenoldopam mesylate is proposed by its sponsor for use in the management of hypertension requiring intravenous (i.v.) treatment (e.g., urgent or emergent hypertension). The drug is manufactured both in and but not marketed in any country.

Appropriate nonclinical studies have been performed to determine the pharmacologic activity and toxicologic potential of fenoldopam. From the results of nonclinical pharmacology studies it can be concluded that the drug is a dopamime receptor agonist exhibiting renal and peripheral vascular vasodilator properties with little or no effect on heart rate. Regarding dopamine receptors, two subtypes ($DA_1$ and $DA_2$) have been characterized in the cardiovascular system. Dopamine receptor agonists are thought to lower blood pressure by vasodilation through action on $DA_1$ receptors or inhibition of sympathetic nerve activity by action on $DA_2$ receptors*. Fenoldopam, unlike dopamine, is relatively selective for postsynaptic dopamine $DA_1$ receptors on vascular smooth muscle.

In the rat and dog, i.v. doses of fenoldopam (7.5 and 15 ug/kg) decrease blood pressure and increase renal blood flow (through vasodilation). In the anesthetized dog, renal vasodilation produced by i.v. doses of 0.1-100 ug/kg occurs even in the presence of alpha-receptor blockade. Renal vasodilation in the dog tends to occur at lower doses (1-3 ug/kg/min i.v. infusion) than required to produce effects on systemic blood pressure and iliac vasculature. Intra-arterial administration of the drug (0.01-3 ug/kg) also causes renal vasodilation and decreases in blood pressure in the dog. Intracoronary injection of the drug in the dog causes direct coronary vasodilation with dose-dependent increases in coronary blood flow.

The vasodilator activity of fenoldopam and degree of selectivity for the renal vascular bed is demonstrated in the spontaneous hypertensive rat and in dog at doses as low as 1.5 and 1 ug/kg i.v., respectively. Numerous in vivo and in vitro pharmacology studies demonstrate the dopamine-receptor mediated activity of fenoldopam and are concisely summarized in tables prepared by the sponsor and included in this review.

The toxicologic evaluation of fenoldopam mesylate, as described in this NDA, included acute, subchronic and chronic (including carcinogenicity) toxicity studies, reprotoxicity studies (FDA Segments I, II and III) and mutagenicity studies. Other nonclinical studies reported included pharmacokinetics, drug interactions, local tolerance of the injectable solution and, special i.v. studies to clarify the mechanism of the vasculotoxic effects associated with the i.v. injection of fenoldopam.

*McCoy, C.E. et al. "Selective Antagonism of the Hypotensive Effects of Dopamine Agonists in Spontaneously Hypertensive Rats" in Hypertension 8(4): 298-302, 1986.

Acute i.v LD-50 values for fenoldopam were estimated to be about 43 and 58 mg/kg, respectively, in rat and mouse. Cyanosis, dyspnea, prostration and respiratory arrest were dose-related and usually noted within 2 to 3 seconds of dosing in both species.

It was concluded from the oral reproductive toxicity studies that fenoldopam (12.5-75 mg/kg/day) produced no adverse effects on general reproductive performance of male and female rats. Oral administration of fenoldopam was neither embryotoxic nor teratogenic in rats at 25-200 mg/kg/day. However, the high-dose caused, in these pregnant rats, a reduction, compared to the control, in their average food consumption and body weight gain and a decrease in the average birth weight of their fetuses. Oral administration of fenoldopam to pregnant rabbits at doses of 6.25-25 mg/kg/day had no maternotoxic, embryotoxic or teratogenic effect. In rat, peri- and postnatal studies showed no adverse effects at oral doses of 25-100 mg/kg.

As for mutagenic potential, fenoldopam was associated with a dose-dependent increase in chromosomal aberrations in vitro in Chinese hamster ovary (CHO) cells. However, there was no such association in vivo in mouse bone marrow. Furthermore, fenoldopam was negative for mutagenic potential in the Ames Salmonella/microsome reverse mutation and the CHO/HGPRT forward mutation assays in vitro and the mouse micronucleous test in vivo.

In a 1-year chronic toxicity study in dog, twice daily oral administration of 5, 10 (raised after 1 month to 12.5), or 20 (raised gradually over time to 60) mg fenoldopam/kg was reported as causing changes consistent with the vasodilator effects of the drug (i.e., redness of the gums, sclera and skin). Although fenoldopam did not induce toxicity in any organ system of the dog, the mean cumulative body weight gained by the high-dose group was about 60% less than gained by the controls.

In a 2-year oral (gavage) carcinogenicity study, fenoldopam doses of up to 35 mg/kg/day (dose reduced from 50 mg/kg after 6 months) administered to Charles River CD-1 mouse had no effect either on the incidence or type of neoplasms observed. An auxiliary group was included in the study to monitor for renal damage because chronic nephritis was observed in mice of a 3-month dose range study after administration of 75 mg fenoldopam/kg/day and higher doses. In the 2-year mouse carcinogenicity study there was a higher incidence of a fibro-osseous lesion of the sternum in the high-dose females when compared to either of two concurrent control groups (p less than 0.05 and 0.01, respectively). There was also an increase in the severity of this lesion in the high-dose mice when compared to the low-, middle-dose or control mice. Although the sponsor reports that the sternal lesion seen in these CD-1 mice is identical histopathologically to sternal lesions reported to occur spontaneously in aging $B6C3F_1$ mice,* the finding has been included in the labeling for this drug.

Another non-neoplastic lesion observed in these chronically treated mice was chronic nephritis (mostly focal and bilateral). Ten male and ten female mice of the auxiliary group were sacrificed after 6 months of dosing with 50 mg fenoldopam/kg/day. The high incidence of chronic nephritis observed in

*Sass, B. and Montali, R., "Spontaneous Fibro-osseous Lesions in Aging Female Mice". Laboratory Animal Science, 50: 907-909, 1980.

the females (8 out of 10) and the absence of this lesion in control females suggested a high probability of increased mortality to mice in the high dose group in the 2-year study. Thus, the 50 mg/kg/day dose administered to mice in the 2-year study was decreased to 35 mg/kg on day 209 for the remainder of the study. Nevertheless, at the end of the 2-year study, chronic nephritis occurred at higher incidence in the mid-dose (25 mg/kg/day) and (significantly higher, p less than 0.0001 using Fisher's Exact Test) in high-dose female mice compared to controls.

Oral administration of fenoldopam to Charles River Sprague-Dawley CD rats by gavage, once daily for 24 months (106 weeks) at dosages of 5, 15 or 25 mg/kg/day (dose increased from 20 mg/kg after about 12 months) had no effect on the incidence of benign (except for an equivocal finding of an increase in mammary gland fibroadenomas in the high-dose females) or malignant neoplasms.

Regarding non-neoplastic lesions in the chronically treated rats, fenoldopam was nephrotoxic in male and female rats of the mid- and high-dose groups (the "no effect" dose was 5 mg/kg/day). A dose-related effect on the incidence and severity of renal pathology was apparent with findings (hyperplasia/hypertrophy of collecting duct epithelium, inflammatory debris in collecting ducts and hyperplasia/hypertrophy of pelvic epithelium at the tip of the renal papilla) believed to be a response to chronic renal injury, possibly related to the 7-beta-glucuronide metabolite of fenoldopam (BUN and creatinine were not examined). An increased incidence of polyarteritis nodosa (affecting arteries of the pancreas, stomach, and testes) in mid- and high-dose male rats and in high-dose female rats was thought to result from the pharmacologic activity of fenoldopam, mediated via activation of the post-junctional dopaminergic $DA_1$ receptor. Although sponsor points out that other drugs (which increase intracellular cAMP via inhibition of phospodiesterase) are also known to cause polyarteritis in the rat (e.g., caffeine or theophylline*) upon long term oral administration, the increased incidence of polyarteritis in high-dose rats of this study leads to the conclusion that fenoldopam has an intrinsic capability of inducing chronic arterial damage in rats upon oral administration.

The remainder of this evaluation will deal with adverse findings associated with i.v. administration of fenoldopam. Repeated dose toxicology studies with fenoldopam given by the i.v. route (bolus and infusion) were performed with rat, dog, rabbit and monkey. Remarkable effects noted in the rat at bolus doses of 24-32 mg/kg/day for 6 days consisted of bradypnea/apnea, diarrhea, body tremors and decreased body weight. The minimum i.v. lethal dose in the rat was 32 mg/kg [LD-50 and 95% Confidence Limits = 49.9 (41.8-59.2)mg/kg]. Dosages of 8-20 mg/kg for 14 days in rat produced vasodilation and transient muscular hypotonia (males only); the apparent "no-effect" dose was 2 mg/kg i.v.

In rat, the arteries are the principal target of drug-induced toxicity following i.v. infusion of fenoldopam. Infusion of fenoldopam (0.1-100 ug/kg/min for 24 hours) produced vasodilation (at 100 ug/kg/min) and dose-related histopathologic lesions (medial smooth muscle necrosis and hemorrhage) in large caliber vessels (greater than 100 um) of the splanchnic and renal vasculature bed (at 1.0 ug/kg/min and above). One high-dose rat developed focal areas of ischemic myocardial necrosis. The "no-effect" dose for these arterial lesions was 0.1 ug/kg/min.

*Johansson, S. "Cardiovascular Lesions in Sprague-Dawley Rats Induced by Long-term Treatment with Caffeine" Acta Path Microbiol Scand Sect A 89:185-191, 1981.

The splanchnic and renal intramedial arterial lesions induced by fenoldopam in rat showed evidence of reversibility (by undergoing repair during the first two weeks after infusion via smooth muscle hyperplasia/hypertrophy) by day 28 post-infusion. However, complete resolution of the arterial lesions did not occur as the large caliber splanchnic/renal arteries still showed evidence of medial hypertrophy and periarterial inflammation.

Infusion of the structurally related drug dopamine (20 ug/kg/min for 1, 4 or 24 hours) in the rat also induced splanchnic arterial lesions (minimal and infrequent in large caliber arteries) that were morphologically identical to those caused by fenoldopam. Dopamine-induced damage to small caliber (less than 100 um) splanchnic arteries (medial fibrinoid necrosis) was completely resolved by day 14 post-infusion.

In the dog, the outstanding effects of i.v. bolus doses of the drug (0.5-8 mg/kg day for 6 days) included vasodilation and dose-related emesis. Infusion with fenoldopam (1-150 mcg/kg/min) for 6 or 24 hours and for 6 hours/day for 14 days produced vasodilation at doses above 1 mcg/kg/min. Other effects noted in the dog included restlessness and salivation at 75 ug/kg/min and slight increases in heart rate at 5 and 50 ug/kg/min. Dose-related emesis, soft stools, mydriasis, buccal and scleral redness occurred at doses of fenoldopam ranging from 5 to 100 ug/kg/min for 6 hours/day for 14 days. Dogs showed no ECG changes or histopathologic arterial lesions. A comparable i.v. infusion study with dopamine (2.5-100 ug/kg/min for 6 and 12 hrs) resulted in marked changes in the ECG at 50 mcg/kg/min and above. At these doses, histopathology examination revealed, in small to medium sized caliber arteries and arterioles, medial smooth muscle necrosis with hemorrhage and in both ventricles, subendocardial hemorrhage accompanied by edema and myocardial necrosis at 50 mcg/kg/min with inconsistent creatinine phosphokinase levels.

In male monkeys, 24 hour i.v. infusions of fenoldopam (5-100 ug/kg/min) induced, at 100 ug/kg/min, slight vasodilation in the faces of 2 of 4 monkeys and sporadic body jerks in one (at 22 hrs of infusion). Notable histopathologic findings were observed in three out of 4 high-dose monkeys. One monkey showed drug-related medial fibrinoid necrosis with minimal intramedial hemorrhage in a few arterioles of the gastric submucosa (comparable with lesion observed in the small caliber arteries following dopamine infusion in rat) and medial necrosis with minimal evidence of hemorrhage in a renal arterial branch; another monkey showed areas of subendocardial and interstitial hemorrhage in the left ventricular papillary muscle and the third monkey had crystalline deposits in the kidney causing minimal tubular epithelial disruption. Although crystalluria (crystals of glucuronide conjugate of fenoldopam) was also detected in mouse at 25 mg/kg/day p.o. and above and in rat at 40 mg/kg/day p.o., sponsor reports that those crystal deposits were dissimilar to the deposits seen in the monkey study. The toxicologic significance to humans of these crystal deposit findings in three different animal species is not clear.

At a meeting with the firm on July 16, 1987, Dr. Lipicky stated that the "urinary crystals of glucuronide of the drug (reported in the rat) was a potential safety concern that should be well addressed in the clinical trials".

Because of the rat's susceptibility to arterial lesions produced by fenoldopam, a series of i.v. infusion studies (infusion durations from 1 up to 24 hours) were conducted to investigate the etiology and pathogenesis of the lesions in rat and to determine the effect, if any, of different variables on the production of these lesions. The results showed that the incidence and severity of the arterial lesions appeared to be related particularly to the duration of the infusion. Ultrastructural examination of the arterial lesions in gastric and pancreatic arteries of rats infused with 5 or 100 ug fenoldopam/kg/min for 24 hours revealed medial smooth muscle cells undergoing pseudovacuolization (of the type associated with vasoconstriction) and medial cell necrosis and hemorrhage. In some areas where the medial smooth muscle cells were affected, although the internal elastic lamina of the arteries was unaffected, there were some areas of damage to the endothelial cells of the vessels. In some areas of endothelial cell damage, red cells and platelets were seen to escape from the arterial lumen into the media through fenestrations in the internal elastic media. Observations by light microscopy raised the concern that the endothelium might be a site of toxic damage. Although in the animal studies there was no reported evidence of arterial intima damage as the site of drug-induced effect, thrombosis may be a possibility in severely affected vessels.

In the rat, infusion of dopamine (5-100 ug/kg/min for 24 hours) was associated with a dose-related increase in MABP and arterial lesions and myocardial fiber damage in all rats at the two highest doses (50 and 100 ug/kg/min). There was a high mortality; only 2/12 rats survived the infusion with 100 mcg/kg/min dopamine. Scanning electron microscopy of arteries of rats infused with fenoldopam or dopamine for 24 hours showed arterial coarctation and corrugation of the luminal surface of arteries, suggestive of segmental vasoconstriction. The findings suggest that in the arterial lesions caused by dopamine and fenoldopam, endothelial damage is progressive and that dopamine causes more extensive endothelial damage than fenoldopam. Focal distribution of lesions, with unaffected segments of arteries lying between damaged ones, suggests that vasoconstriction may be involved in the pathogenesis of the arterial lesions. Arterial lesions produced by 24-hour infusions of the R- and S- isomers of fenoldopam and other benzazepines were identical to those described with 24-hour infusion of the racemic fenoldopam (e.g., intramural hemorrhage and medial necrosis in arteries of renal and splanchnic vascular beds). The co-administration of other drugs with fenoldopam did not alter the morphology of the arterial lesions induced by fenoldopam alone.

Regarding the pathogenesis of arterial lesions caused by fenoldopam, the use of a selective dopamine $DA_1$ receptor antagonist (SK&F 83566-C), prevented and attenuated the fenoldopam arterial lesion. This finding suggests that activation of post-junctional dopaminergic $DA_1$ receptors is causally associated with the induction of fenoldopam medial necrosis and hemorrhage in large caliber (100-800 um) arteries in rat. Further, co-administration of phenoxybenzamine and either fenoldopam or dopamine increased the incidence and severity of the hemorrhagic lesions in large caliber arteries indicating that maintenance of vascular tone or some interaction between $DA_1$ and alpha-adrenoceptors plays a role in the induction of these types of lesions. Finally, in rat, concurrent administration of phenoxybenzamine, SK&F 83566-C and dopamine, eliminated the fibroid lesions of small vessels and the hemorrhagic lesions in larger arteries induced by dopamine.

The rat appears to be uniquely susceptible to the arterial toxicity induced by dopaminergic agents; such lesions were not seen in the dog or the monkey at i.v. dosages up to 100 ug/kg/min. This dose is at least 50 to 100 times the recommended human i.v. infusion dosage (range 0.1 to 1.6 ug/kg/min) which is said to be efficacious in reducing blood pressure without any adverse effect on the peripheral vasculature.

Pharmacokinetics and metabolism of fenoldopam have been reported for mouse, rat, dog, monkey and man. Following i.v. infusion of the drug in rat, dog and man, steady-state plasma concentrations of the drug were achieved, usually within 30 to 60 minutes after the start of infusion with mean steady-state plasma concentrations proportional to infusion rate (Table 7).

Following i.v. administration, the elimination half-lives of fenoldopam in the rat and dog were approximately 10 and 12 minutes, respectively. The alpha disposition half-life in man, accounting for 97% of the total area under the curve, was approximately 6 minutes. Albumin appears to be the major binding protein in plasma in all species studied.

Fenoldopam is metabolized in the liver. In mouse, rat, dog and monkey i.v. administered fenoldopam was excreted in the urine and feces as the unchanged drug and metabolites. The urinary metabolic profile of fenoldopam (Table 9) indicated that the same metabolic pathways were utilized by the species studied, although quantitative differences were noted between species and route of administration. The major metabolic pathway for fenoldopam in the mouse, rat and man was the 7-beta-glucuronide (insignificant in the monkey and dog). Sulfate conjugation was a major pathway in dog and man and a minor pathway in the mouse, rat and monkey. In mouse, rat, dog and man, O-methylation to form 7- and 8-methoxy fenoldopam was a minor pathway following oral or i.v. administration (the methoxy derivatives were not measured in monkey). These methoxy metabolites were mainly conjugated as sulfates in the dog but were only partially conjugated in the mouse and rat. Various studies suggest only weak activity with the methoxy and glucuronide metabolites. As for the 7- and 8-sulfate metabolites (SK&F 87783 and SK&F 87782, respectively), i.v. infusion at high doses (100 to 1000 times equieffective doses of fenoldopam) did increase the RBF in conscious dog with no effect on HR. This finding suggests that in the dog, the sulfate metabolites undergo in vivo conversion back to fenoldopam.

In conclusion, fenoldopam is a benzazepine derivative structurally related to dopamine. Nonclinical testing with the drug has been extensive; toxicity studies followed FDA guidelines. The results submitted show that fenoldopam is a vasodilator drug which dilates both renal and peripheral vascular beds with little or no effect on heart rate. Unlike dopamine, the drug is relatively selective for postsynaptic dopamine $DA_1$ receptors on vascular smooth muscle. Fenoldopam, as an injectable formulation, is proposed for the management of hypertension in patients requiring prompt control by i.v. therapy. In the species studied, oral administration of fenoldopam showed no carcinogenic potential, no teratogenic potential and no reproductive toxicity. Although in vitro the drug was associated with chromosomal

aberrations in CHO cells, there was no evidence of mutagenicity in other in vitro and (one) in vivo tests. In the species studied, continuous i.v. administration of fenoldopam showed the rat to be uniquely sensitive to drug-induced arterial lesions of large caliber splanchnic and renal arteries. Histopathologic examination of these arteries of rats infused for 24-hours with fenoldopam revealed intramedial cell damage, sometimes accompanied by endothelial cell damage. Damage to endothelial cells was evident in the gastric serosal arteries of 3/16 rats infused at 100 ug/kg/min for 24 hrs (medial necrosis and hemorrhage were advanced in these animals). The drug is metabolized in the liver; the major metabolite of fenoldopam in the mouse, rat and man is the 7-beta-glucuronide.

After repeated oral doses of fenoldopam, a common finding in rat and mouse was crystalluria (crystals identified as 7-beta-glucuronide). Regarding consistency of toxic effects induced by fenoldopam, crystalluria in two (possibly three) animal species is remarkable. In rat, when fenoldopam was administered orally there was a consistent pattern of renal toxicity in subchronic and chronic studies with the total daily doses required to induce nephrotoxicity reduced with increasing duration of exposure. Clinical chemistry measurements indicated an increase in serum BUN and creatinine in the 3-month study but there was no increase in these parameters in the 12-month study; no clinical chemistries were performed in the 18-month or 2-year studies. Regarding the nephrotoxicity in the 2-year rat study, an increase in the incidence and severity of hyperplasia/hypertrophy of collecting duct epithelium at the tip of the renal papilla was most evident at the high-dose. Although chronic nephritis was reported in both control and fenoldopam treated mice in the 2-year carcinogenicity study, the incidence/severity of the nephritis was significantly greater (p less than 0.01) in the females of the high-dose group (50 mg/kg/day reduced to 35 mg/kg/day on day 210).

RECOMMENDATIONS:

1. NDA 19-922 for fenoldopam mesylate injection is approvable from the preclinical viewpoint.

2. The labeling is inadequate from the standpoint of content of the section on "Carcinogenesis, Mutagenesis, Impairment of Fertility". (See recommended wording under Labeling .)

Estela A. Gonzalez Barry

Attachments I and II

cc:
Orig NDA
HFD-502/JWeissinger
HFD-345/GJames
~~HFD-110~~
HFD-110/CSO
~~HFD-110/EBarry~~
eb/7/13/89/0044B
clb/8/23/89;11/29/89;6/28/90;8/2/90;8/30/90

NDA 19-922 ıoldopam Injection
.tachment I)

A Brief Coversheet for Carcinogenesis Study Review

1. Species & Strain — Mouse (CD-1)

2. Name of laboratory

3. No./sex/group — 100

4. Doses (O,L,M,H)*

| Control I | Control II | LD | MD | HD** |
|---|---|---|---|---|
| 0 (deionized water) | 0 | 12.5 | 25 | 50-35 mg/kg/day (reduced) to 35 mg/kg after 6 months) |

5. Basis for dose selection stated yes X
no ___

6. Interim Sacrifice yes ___
no X**

7. Total Duration (months) — 24

8. No. Alive at termination (O,L,M,H)

| | Control I | Control II | LD | MD | HD |
|---|---|---|---|---|---|
| Males | 62 | 61 | 63 | 63 | 51 |
| Females | 45 | 49 | 57 | 50 | 45 |

9. Statistical Methods Used — Difference between control and treated group lesions were tested using both Yate's Corrected Chi-Square[1] and Fisher's Exact Test[2].


1. Daniel, W. (1974). Biostatistics: A Foundation for Analysis in the Health Sciences. John Wiley & Sons, Inc.

2. Steel, R. and Torrie, J.H. (1980). Principles and Procedures of Statistics: A Biometrical Approach, 2nd Ed., McGraw-Hill, New York.


10. Tumor and non-tumor data for each tissue attached.

*Fenoldopam base
**To monitor for drug-induced renal changes, an auxiliary high-dose group (10 M, 10 F) was included. These mice were killed after 6 months and their kidneys examined. When chronic nephritis was found (only in the females), the high-dose was decreased from 50 to 35 mg/kg/day on day 209 of study.